SMDM 2021

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Short course:

Cost-effectiveness analysis with probabilistic graphical models

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Disclaimer

- We are the developers of OpenMarkov, an open-source tool for probabilistic graphical models (PGMs), which we will present in this course; so, we may be biased when comparing it with other software tools.
- We have founded *DeciSupport AI*, a spin-off that offers consultancy about modeling for medical decision analysis (especially with OpenMarkov and R), courses, software development, etc.

OVERVIEW

1. Introduction
2. Probabilistic diagnosis
3. Bayesian networks
4. Unicriterion decision analysis
5. Multicriteria decision analysis
6. Temporal models
7. Sensitivity analysis
8. Software tools for CEA
9. Conclusion

1. Introduction: history of PGMs

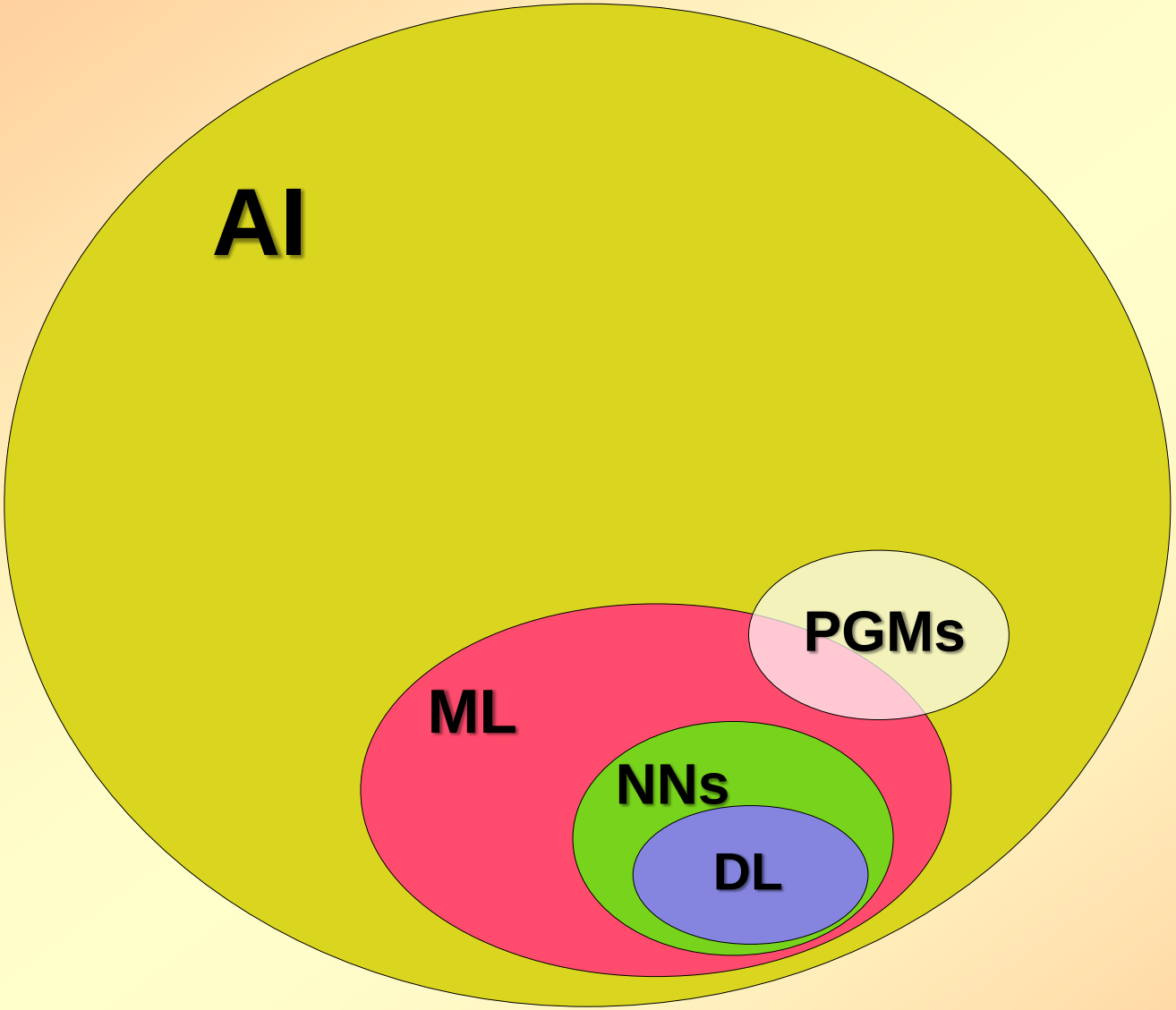
History of PGMs

"Born" in the field of A.I.

- Markov chains: A. Markov, 1906
- Probabilistic models for genetics: S. Wright, 1921
- Markov decision processes (MPDs): R. Bellman, 1957
- Naïve Bayes method: three independent papers, 1963
- Partially observable MDPs (POMDPs): K. Åström, 1965
- Influence diagrams: R. Howard, J. Matheson, 1980, 1984
- Bayesian networks: J. Pearl, 1982, 1986, 1988
- Dynamic Bayesian networks: T. Dean, K. Kanazawa, 1989
- Factored MDPs: C. Boutilier et al., 1995, 2000
- Factored POMDPs: C. Boutilier, D. Poole, 1996
- Decision analysis networks: F.J. Díez et al., 2012
- Markov influence diagrams: F.J. Díez et al., 2015, 2017

Nowadays PGMs are one of the main techniques used in A.I.

Some areas of AI



ML = machine learning

NNs = neural networks

DL = deep learning

PGMs = probabilistic graphical models

2. Probabilistic diagnosis

2.1. Basic concepts of probabilistic diagnosis

Basic concepts for medical diagnosis

- Disease *E*, result of a test *T*
- Probabilistic parameters (model inputs):
  - Prevalence: $P(+e)$
  - Sensitivity: $P(+t|+e)$
  - Specificity: $P(\neg t|\neg e)$
- Predictive values, i.e., probability of the disease when knowing the result of the test (model outputs):
  - Positive PV: $P(+e|+t)$
  - Negative PV: $P(\neg e|\neg t)$

2.1. Bayes theorem

Bayes theorem

- We knew that

$$P(x|y) = \frac{P(x,y)}{P(y)}$$ by the definition of $P(x|y)$

$$P(x,y) = P(x)\cdot P(y\,|\,x)$$ by the definition of $P(y|x)$

$$P(y) = \sum_x P(y|x)\cdot P(x)$$ by the theorem of total prob.

- Combining these results:

$$P(x|y) = \frac{P(x,y)}{P(y)} = \frac{P(x)\cdot P(y|x)}{P(y)} = \frac{P(x)\cdot P(y|x)}{\sum_{x'} P(x')\cdot P(y|x')}$$

- It means that knowing $P(x)$ and $P(y|x)$ we compute $P(x|y)$.

Predictive value of a finding

- Positive predictive value: $P(+e|+h)$

$$P(+e|+h) = \frac{P(+e)\cdot P(+h|+e)}{P(+e)\cdot P(+h|+e) + P(\neg e)\cdot P(+h|\neg e)}$$

$$\text{PPV} = \frac{\text{prev}\cdot\text{sens}}{\text{prev}\cdot\text{sens} + (1-\text{prev})\cdot(1-\text{spec})}$$

- Negative predictive value: $P(\neg e|+h)$

$$P(\neg e|\neg h) = \frac{P(\neg e)\cdot P(\neg h|\neg e)}{P(+e)\cdot P(\neg h|+e) + P(\neg e)\cdot P(\neg h|\neg e)}$$

$$\text{NPV} = \frac{(1-\text{prev})\cdot\text{spec}}{\text{prev}\cdot(1-\text{sens}) + (1-\text{prev})\cdot\text{spec}}$$

Hands-on exercise 1

- Example:
  - Prevalence of a disease: 14%
  - Sensitivity of a test: 70%
  - Specificity of the test: 91%

- Questions:
  - What is the positive predictive value (PPV)?
    - If the test is positive, what is the probability that the patient has the disease?
  - What is the negative predictive value (NPV)?
    - If the test is negative, what is the probability that the patient does *not* have the disease?

OpenMarkov

OpenMarkov is a software tool for probabilistic graphical models (PGMs) developed by the Research Centre for Intelligent Decision-Support Systems of the UNED in Madrid, Spain.

It has been designed for:

- editing and evaluating several types of several types of PGMs, such as Bayesian networks, influence diagrams, factored Markov models, etc.;
- learning Bayesian networks from data interactively;
- cost-effectiveness analysis.

You can read the tutorial to have a glimpse of its capabilities.

Visit the **users' page** to download **OpenMarkov** and obtain additional information.

OpenMarkov. Main features

- Main advantage: open source
  - Free
  - Users can adapt it to their needs
  - Software engineering tools:
    JUnit, maven, mercurial (bitbucket), nexus, bugtracker, etc.
- Strengths
  - Written in Java: portability (Windows, linux, MacOS…)
  - Many types of models, potentials, etc.
  - Algorithms not available in any other package
    - CEA with IDs and DANs
    - interactive learning
  - Very active: new features are continuously added
  - Support for users and developers: wiki, lists, mail…
  - Well-documented format for encoding networks: ProbModelXML.

Networks

Probabilistic networks encoded in the format **ProbModelXML**. They have been created with OpenMarkov's graphical user interface; this program can be used to open and edit them. The technical report that specifies the **ProbModelXML** format contains references for each type of network.

Bayesian networks

- Two diseases
- Asia [Lauritzen and Spiegelhalter, 1988]
- Alarm [Beinlich et al., 1989]

Decision analysis networks

- Decision about test (unicriterion)
- The used car buyer problem [Howard, 1984]
- The reactor problem [Covaliu et al., 1995]
- The dating problem [Nielsen et al., 2000]
- The king's problem [Jensen et al., 2002]
- The diabetes problem [Demirer et al., 2006]
- *n*-test problem: 3 tests, 4 tests, 5 tests, 6 tests, 7 tests
- Mediastinet (unicriterion) [Luque, 2009]

Influence diagrams

- Decision about test (unicriterion)
- Cost-effectiveness of a test and two therapies
- Mediastinet (unicriterion) [Luque, 2009]
- Mediastinet (cost-effectiveness) [Luque, 2009]
- Arthronet (unicriterion) [León, 2011]
- Arthronet (cost-effectiveness) [León, 2011]

Markov influence diagrams

- Cost-effectiveness of two therapies for HIV [Chancellor et al., 1997], new version
- Cost-effectiveness of a new type of hip prosthesis [Briggs et al., 2004]
- Cost-effectiveness of HIV prophylaxis in children [Ryan et al., 2008]
- Cost-effectiveness of the HPV vaccine [Callejo et al., 2010], version without super-value nodes
- Cost-effectiveness of bilateral cochlear implantation [Pérez-Martín et al., 2016]
- Cost-effectiveness of colorectal cancer screening [Lalana et al., 2016]

POMDPs

OpenMarkov. Limitations

- Main weakness
  - Still a prototype: needs debugging
- Other weaknesses
  - Written in Java: relatively slow (in some cases)
  - No on-line help, documentation still poor
  - Support is limited, due to scarcity of human resources.

Probabilistic diagnosis with two findings

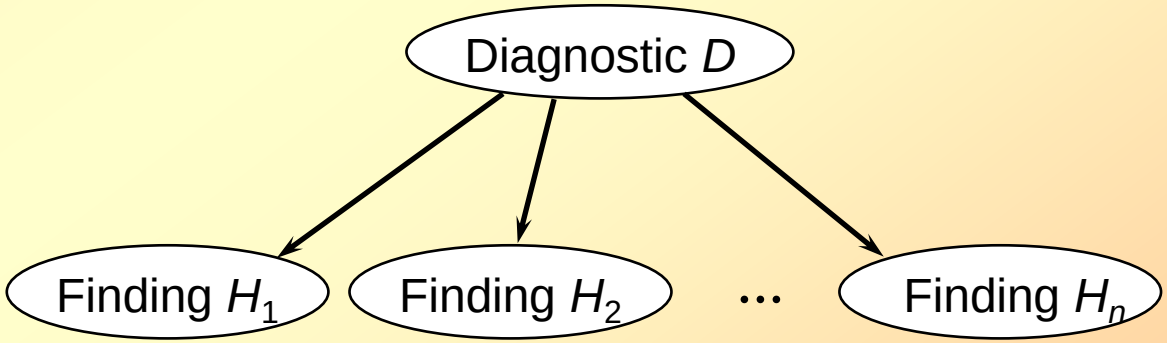
- Example:
  - Prevalence of the disease: 14%
  - Sensitivity of test C: 70%
  - Specificity of test C: 91%
  - Sensitivity of test E: 90%
  - Specificity of test E: 93%
- Question:
  - What is the posterior probability for each combination of findings?

2.2. The naïve Bayes method

The naïve Bayes method

- Two hypotheses:
  - Diagnostics are mutually exclusive
    $\Rightarrow$ every patient has at most one disease
  - Findings are conditionally independent given the diagnostics

- Graphical representation:



Succesfull applications of the naïve-Bayes

- Lodwick GS, Haun CL, Smith WE, et al. , "Computer diagnosis of primary bone tumors: A preliminary report" *Radiology* **80** (1963) 273-275.
- Overall JE, Williams CM, "Conditional probability program for diagnosis or thyroid function" *JAMA* **183** (1963) 307-313.
- Toronto AF, Veasy LG, Warner HR, "Evaluation of a computer program for diagnosis of congenital heart disease" *Progress in Cardiovascular Diseases* **5** (1963) 362-377.

  Warner HR, Toronto AF, Veasy LG, "Experience with Bayes' theorem for computer diagnosis of congenital heart disease" *Annals New York Acad. Sciences* **115** (1964) 558-567.
- de Dombal FT, Leaper JR, Staniland JR, et al., "Computer-aided diagnosis of acute abdominal pain" *BMJ* **2** (1972) 9-13.
- Gorry GA, Kassirer JP, Essig A, Schwartz WB, "Decision analysis as the basis for computer-aided management of acute renal failure" *Amer. J Med* **55** (1973) 473-484.
- Gorry GA, Silverman H, Pauker SG, "Capturing clinical expertise: A computer program that considers clinical responses to digitalis" *Amer. J. Med* **64** (1978) 452-460.

More accurate than medical doctors (in restricted domains).

Limitations of the naïve Bayes

- In general, the diagnostics are not mutually exclusive.
  - The naïve Bayes cannot diagnose that more than one diseases are present
- In general, findings are not conditionally independent.
  - The naïve Bayes gives wrong results when findings are (conditionally) correlated.

We'll come back to this later on.

Let's first see how Bayesian networks address this problem.

3. Bayesian networks

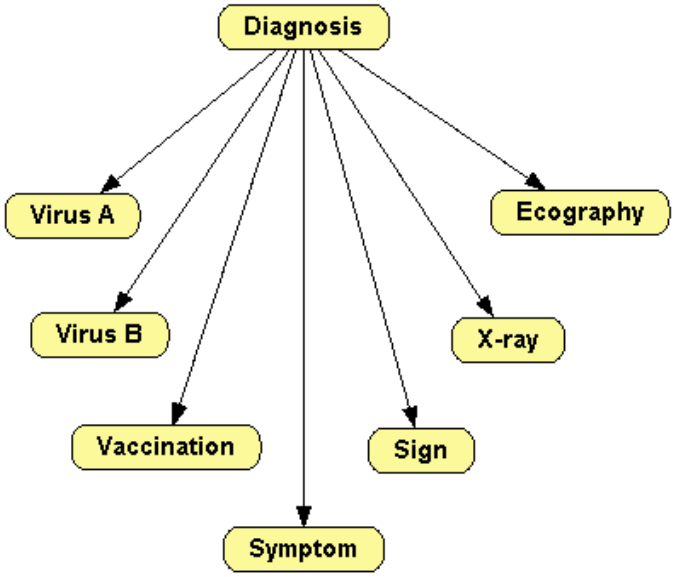
Definition of Bayesian network

- Elements:
  - a set of variables $\{X_i\}$
  - an acyclic directed graph
    - every node in the graph represents a variable X_i
  - a conditional probability distribution (usually a table) for each variable: $P(x_i \mid pa(x_i))$
    - for a node without parents: $P(x_i \mid pa(x_i)) = P(x_i)$

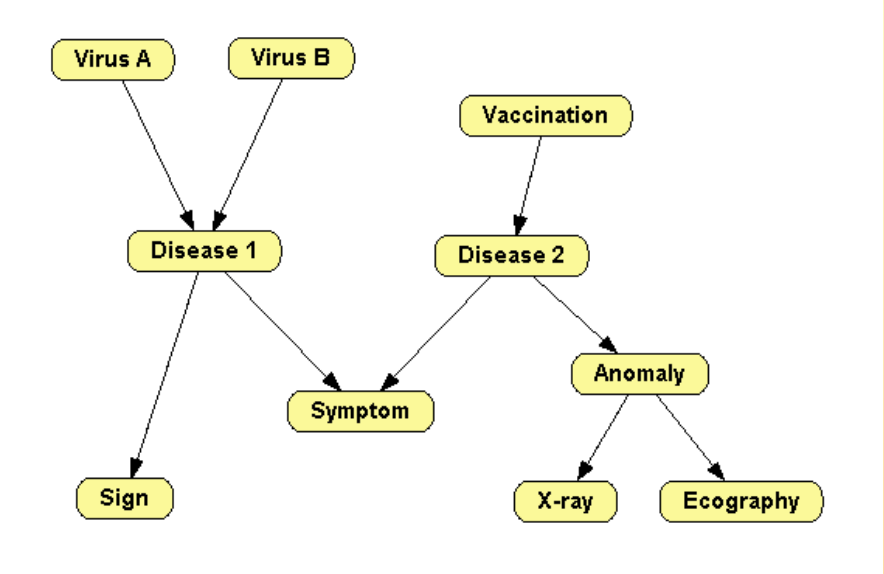
- Result: join probability for the network

$$P(x_1, \cdots, x_n) = \prod_{i=1}^{n} P(x_i \mid pa(x_i))$$

Naïve Bayes



Bayesian network

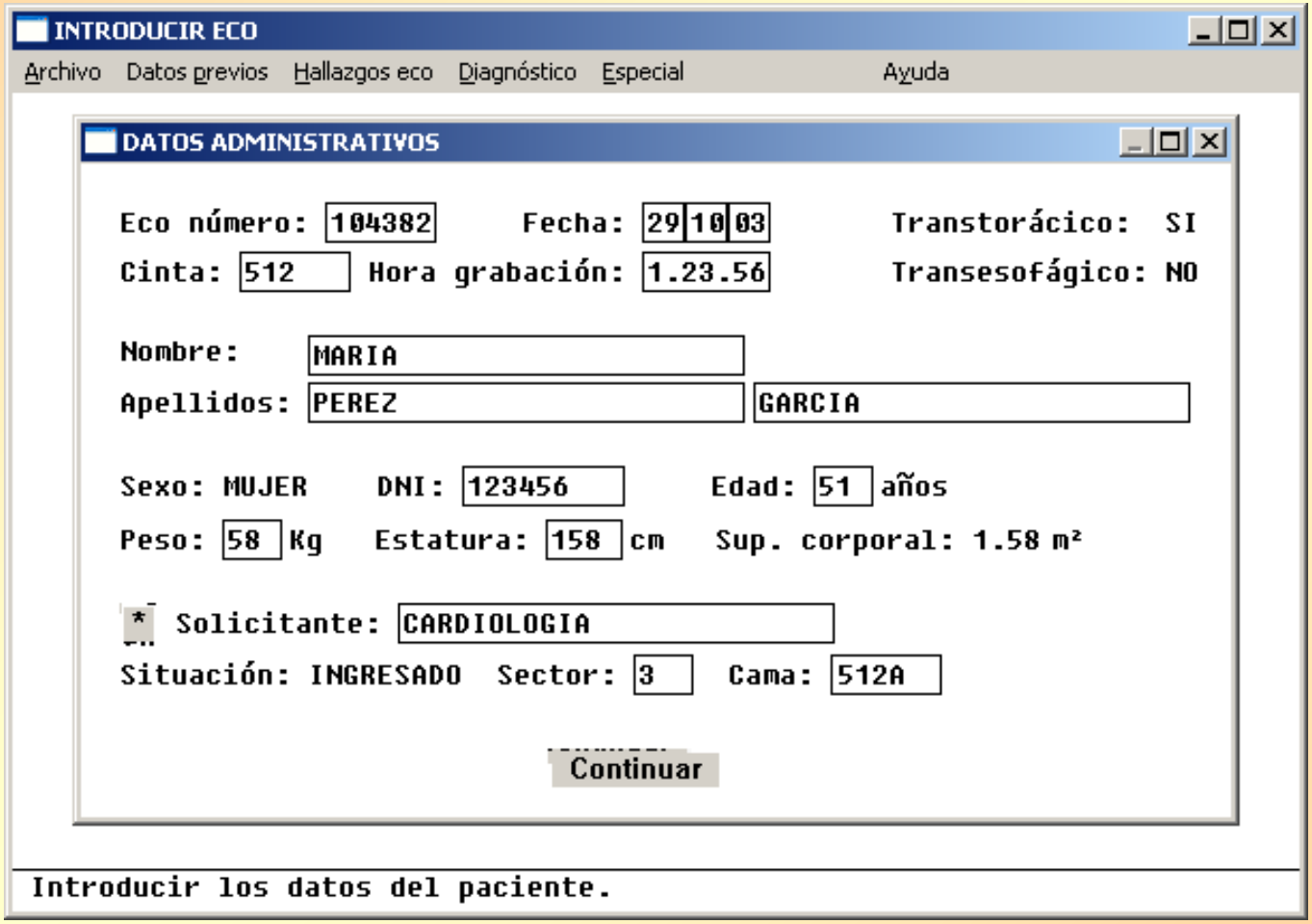


3.2. Examples of BNs

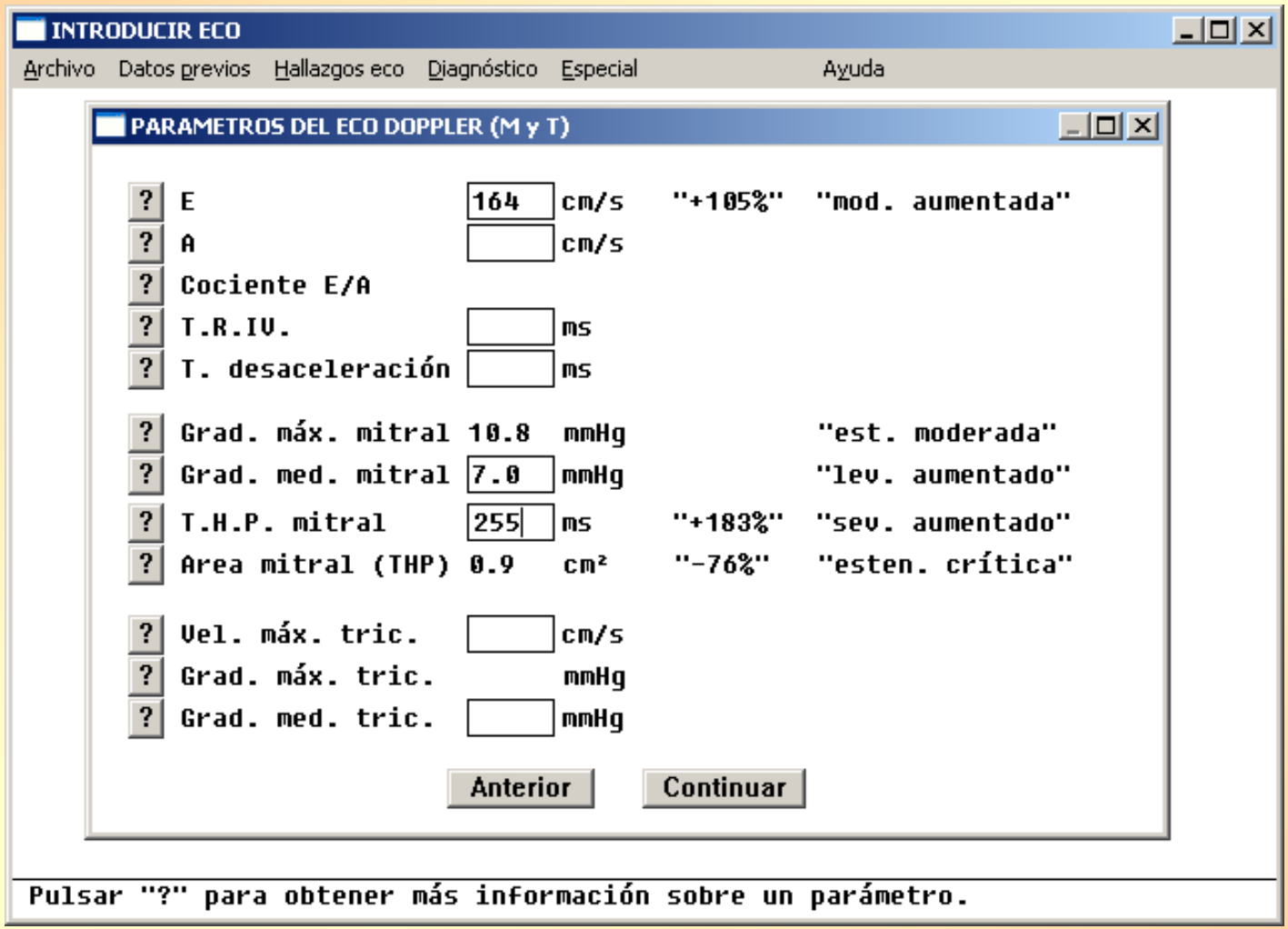
Examples of BNs

- Medical Bayesian networks we have built
  - DIAVAL: echocardiography (valvulopathies)
    F. J. Díez' thesis, 1994
  - Prostanet: urology (prostate cancer)
    Carmen Lacave's thesis, 2003
  - Nasonet: nasopharyngeal cancer spread
    Severino Galán's thesis, 2003
  - HEPAR II: liver diseases
    Agnieszka Onisko's thesis, 2003
  - Catarnet: Cataract surgery
    Nuria Alonso's thesis, 2009

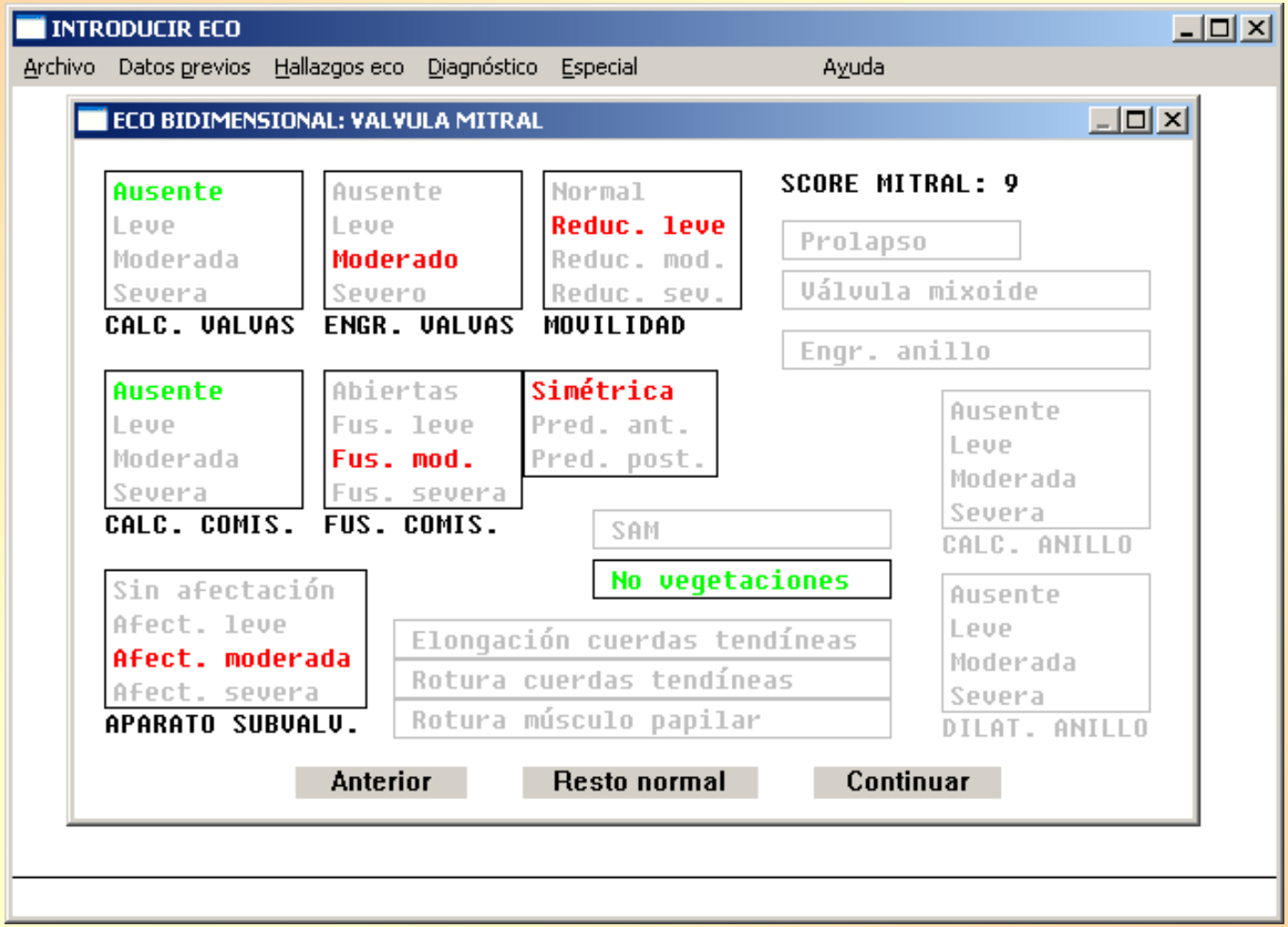
DIAVAL


INTRODUCIR ECO
Archivo
Datos previos
Hallazgos eco
Diagnóstico
Especial
Ayuda
DATOS ADMINISTRATIVOS
Eco número: 104382
Fecha: 29 10 03
Transtorácico: SI
Cinta: 512
Hora grabación: 1.23.56
Transesofágico: NO
Nombre: MARIA
Apellidos: PEREZ
GARCIA
Sexo: MUJER
DNI: 123456
Edad: 51 años
Peso: 58 Kg
Estatura: 158 cm
Sup. corporal: 1.58 m²
* Solicitante: CARDIOLOGIA
Situación: INGRESADO
Sector: 3
Cama: 512A
Continuar
Introducir los datos del paciente.

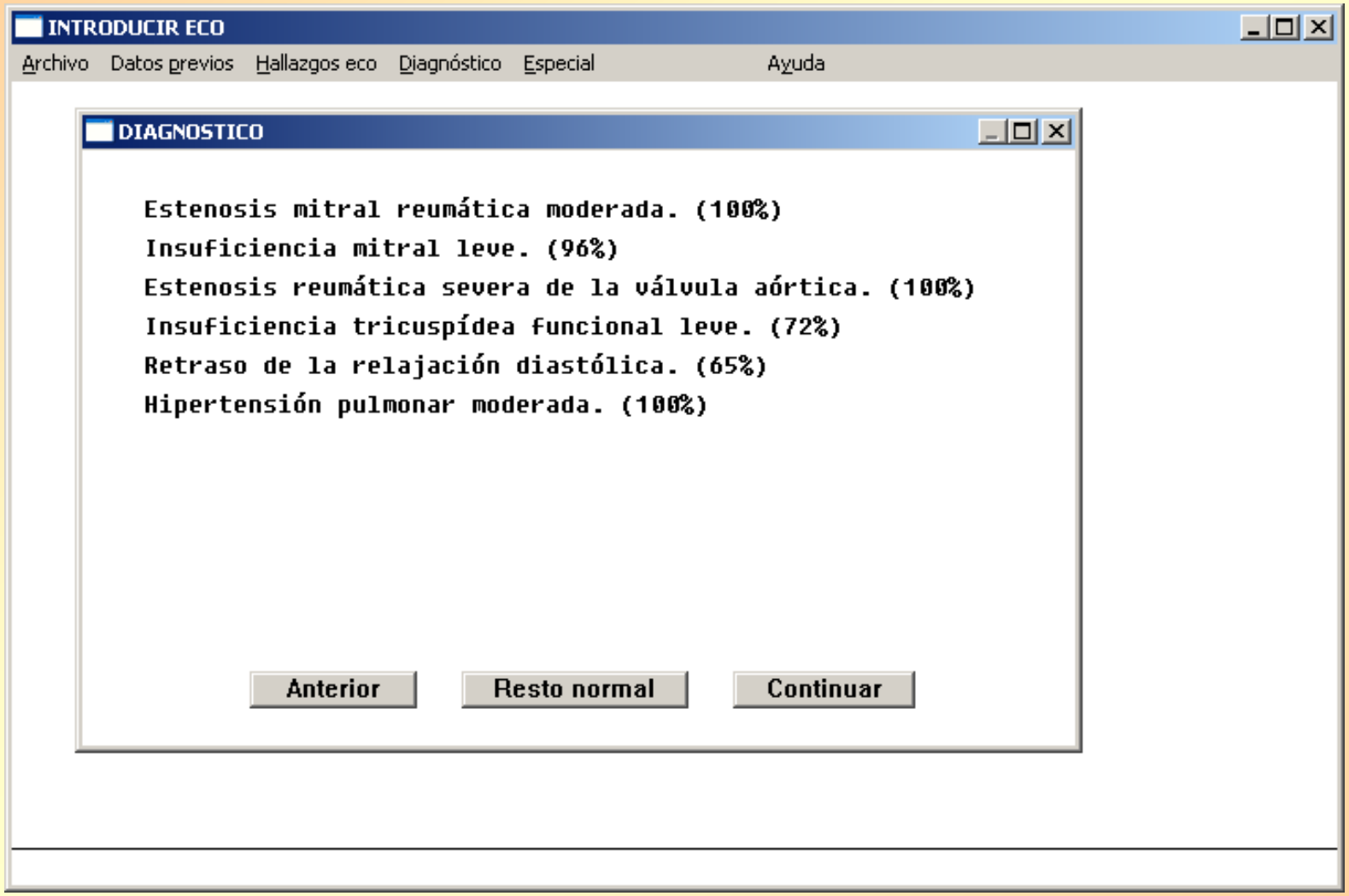
DIAVAL: numeric findings



DIAVAL: qualitative findings



DIAVAL: diagnostics



DIAVAL: final report

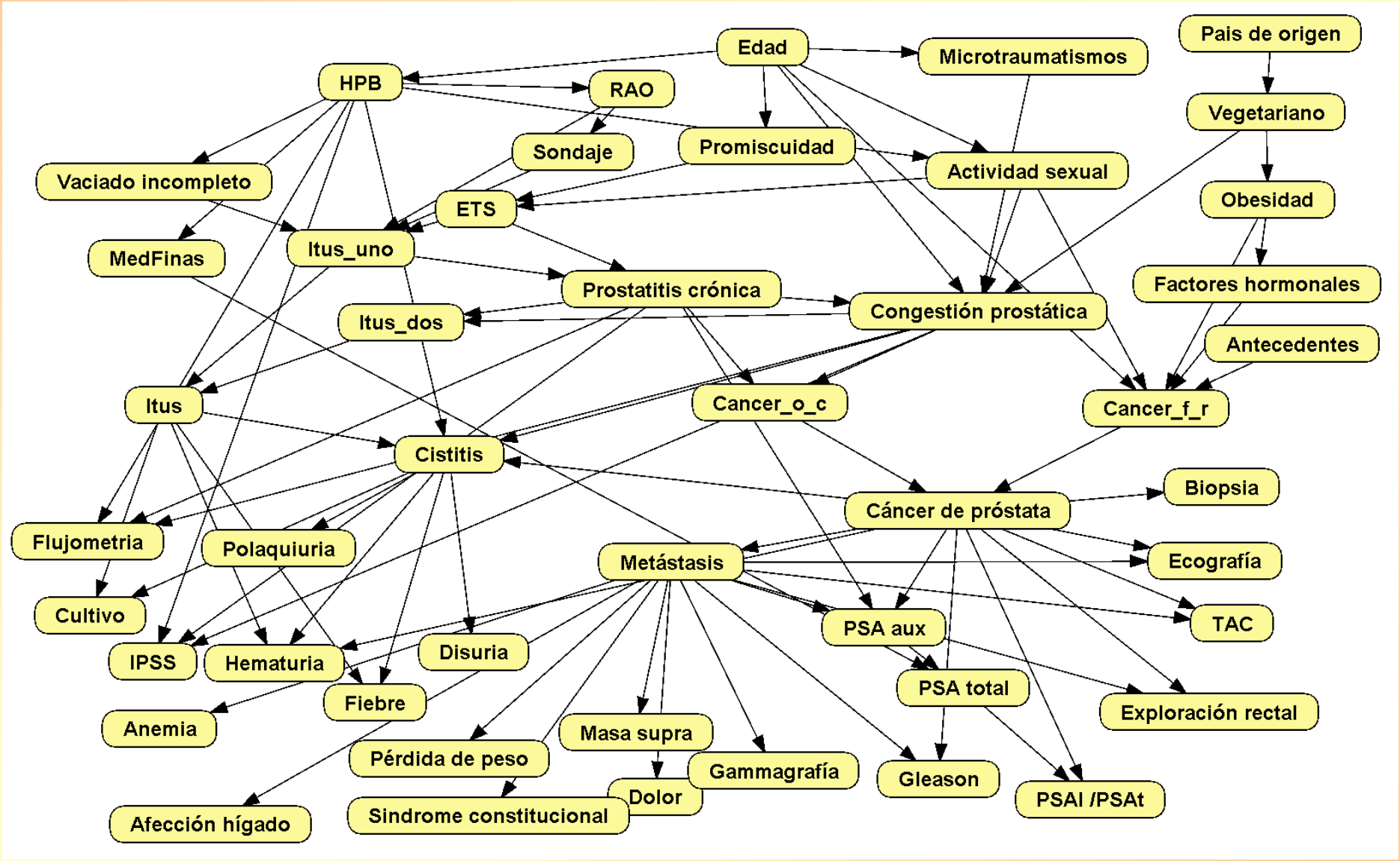
in a text editor

INFORME.TXT - Bloc de notas

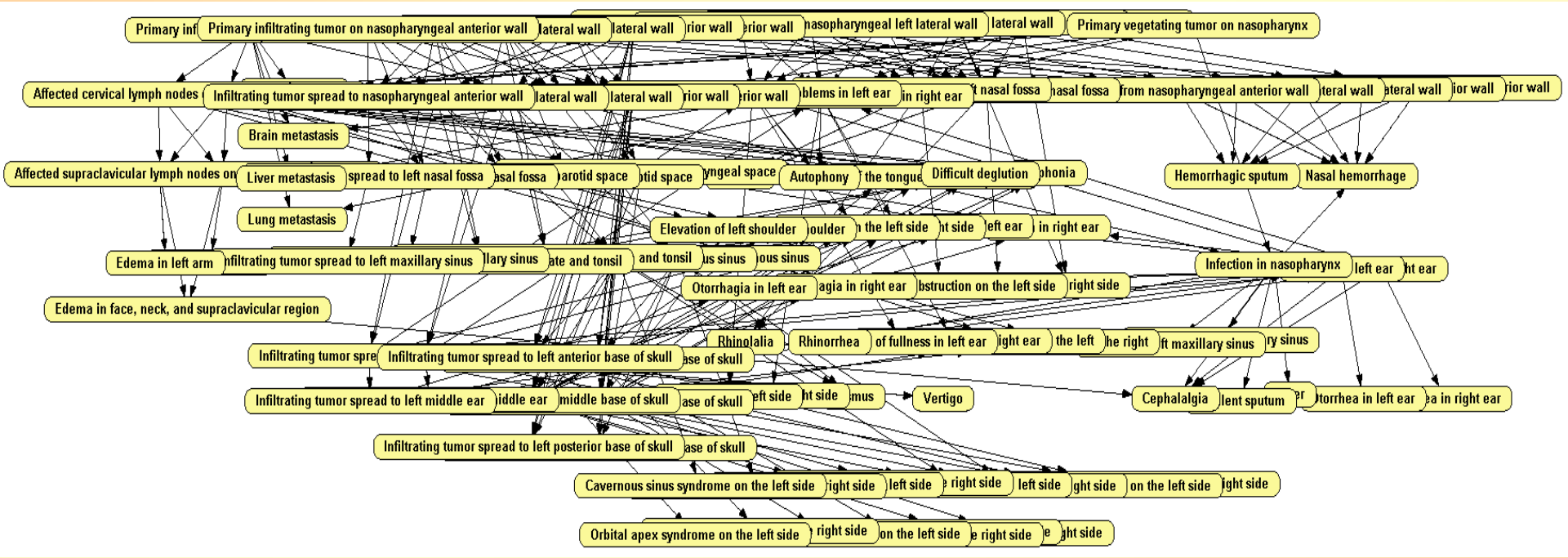
Archivo Edición Formato Ver Ayuda

```
Datos administrativos
=====================
  Nº eco: 104382.  Fecha: 29/10/3.  Cinta: 512.
  MARIA GARCIA PEREZ.  DNI: 1234567.
  Edad: 51 años.  Mujer.
  Peso: 58 Kg.  Estatura: 158 cm.  Sup. corporal: 1.58 m².
  Solicitante: CARDIOLOGIA.
  Ingresada, sector 3, cama 512A.

Síntomas
=========
  Disnea de grado II.

Válvula mitral
==============
  Area (eco 2D): 1.2 cm².
  Velocidad onda E: 164 cm/s.
  Gradiente máximo: 10.8 mmHg.
  Gradiente medio: 7.0 mmHg.
  Tiempo de hemipresión: 255 ms.
  Area (THP): 0.9 cm².
  Engrosamiento moderado de las valvas.
  No calcificación de las valvas mitrales.
  Reducción leve de la movilidad.


[...]


Contractilidad segmentaria normal.

Pericardio normal.

DIAGNOSTICO
===========
  Estenosis mitral reumática moderada.
  Insuficiencia mitral leve.
  Estenosis reumática severa de la válvula aórtica.
  Insuficiencia tricuspídea funcional leve.
  Retraso de la relajación diastólica.
  Hipertensión pulmonar moderada.


                    Dra. Elena Iturralde  |
```

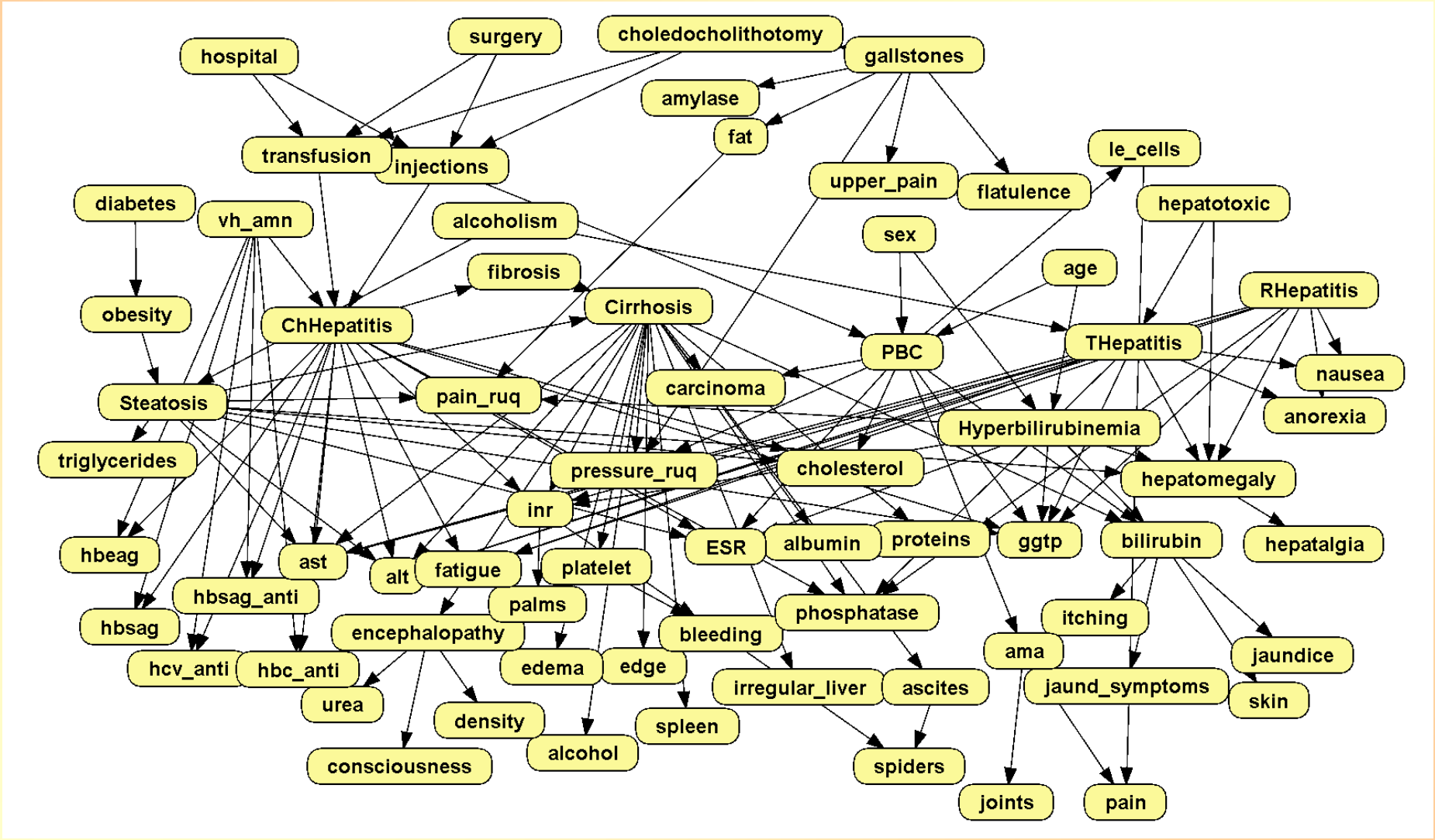
Prostanet (for prostate diseases)



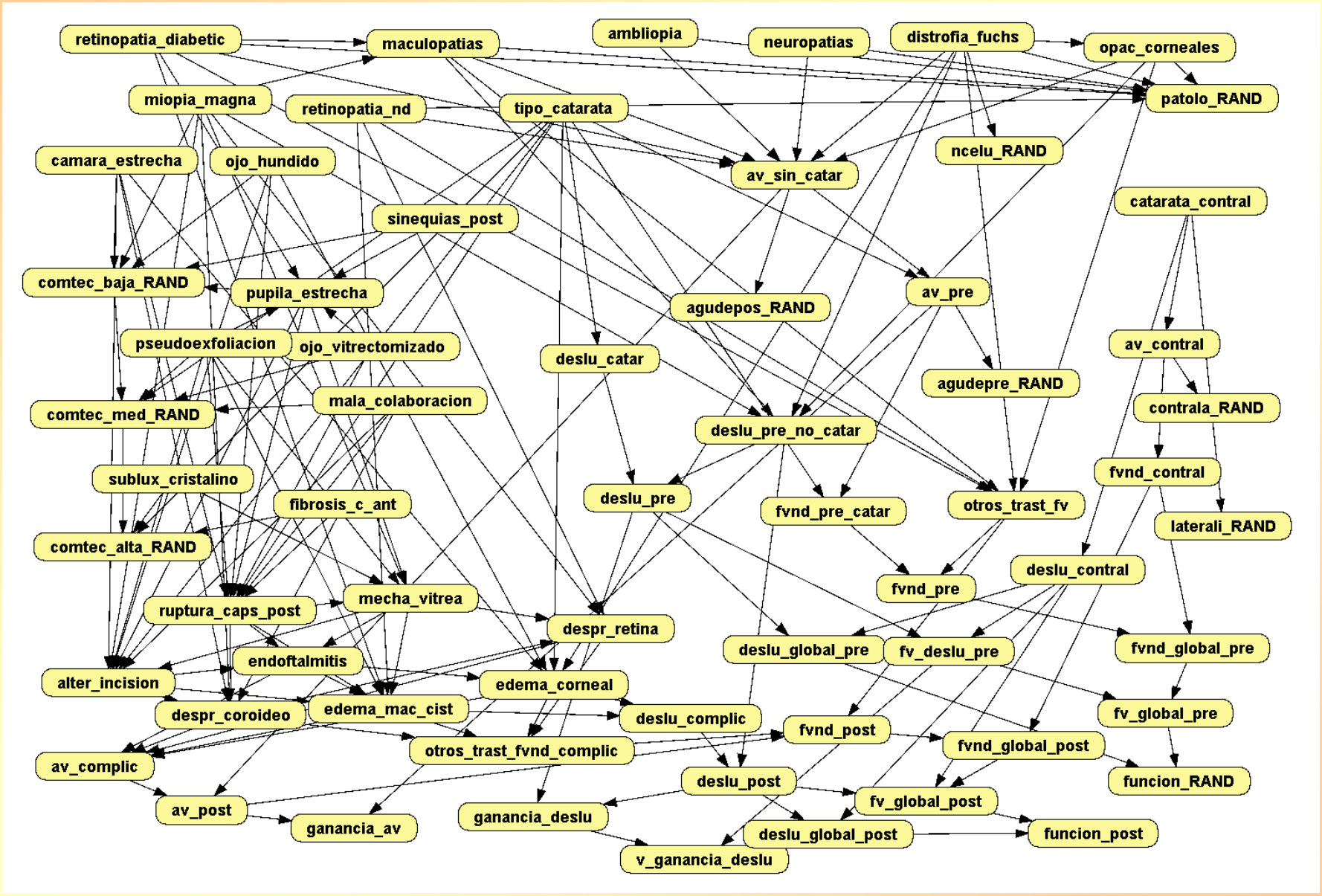
Nasonet (nasopharyngeal cancer spread)



Hepar II (liver diseases)

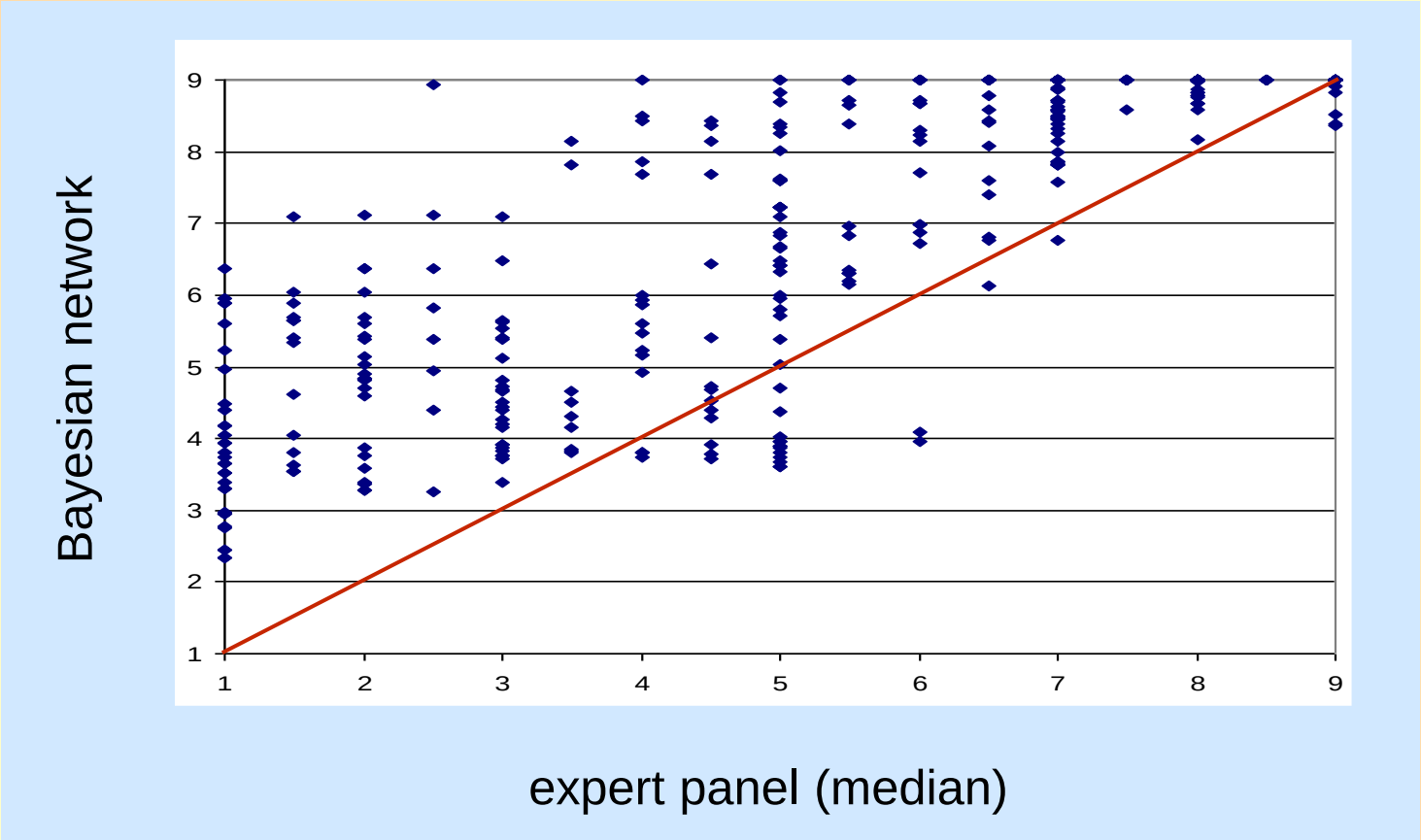


Catarnet (cataract surgery)



BN vs. a panel of experts (Delphi)

- Comparison in 429 clinical scenarios



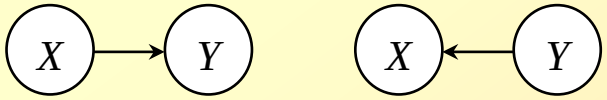
- Result: ICC=0.83 [IC95%: 0.80 – 0.86] (p<0.001)

3.3. BNs and causality

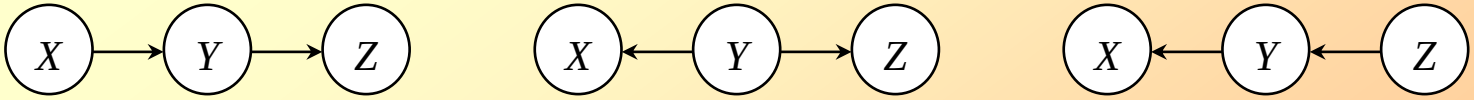
Two interpretations of BNs

- Semantics of a Bayesian network:
  - As a mathematical model: probabilistic independencies
  - As a model of the real world: they usually represent causality
- Two BNs are mathematically equivalent when they represent the same set of independencies.
- But two different BNs can never have the same causal meaning.

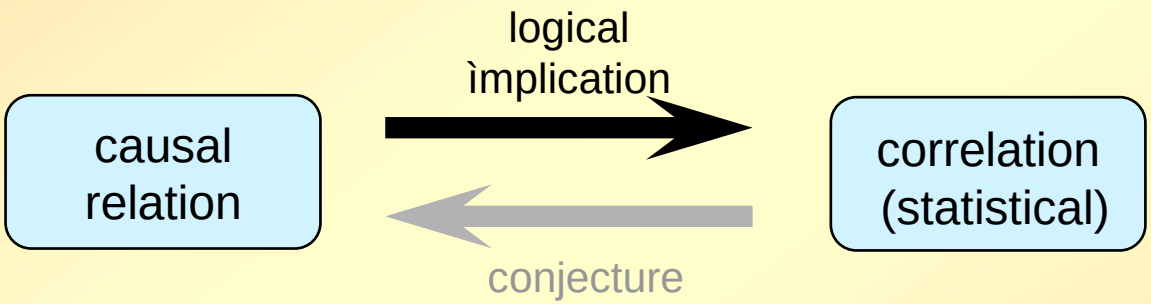
- Example 1



- Example 2

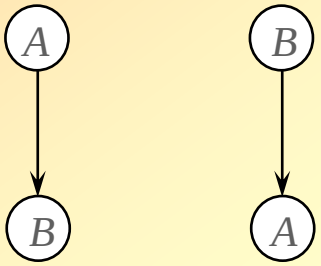


Correlation does not imply causality

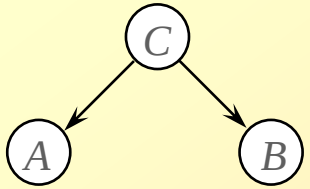


Several types of correlation

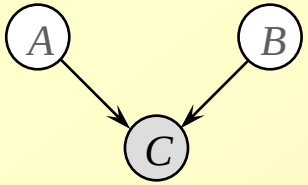
- Direct cause



- Common cause



- Selection bias



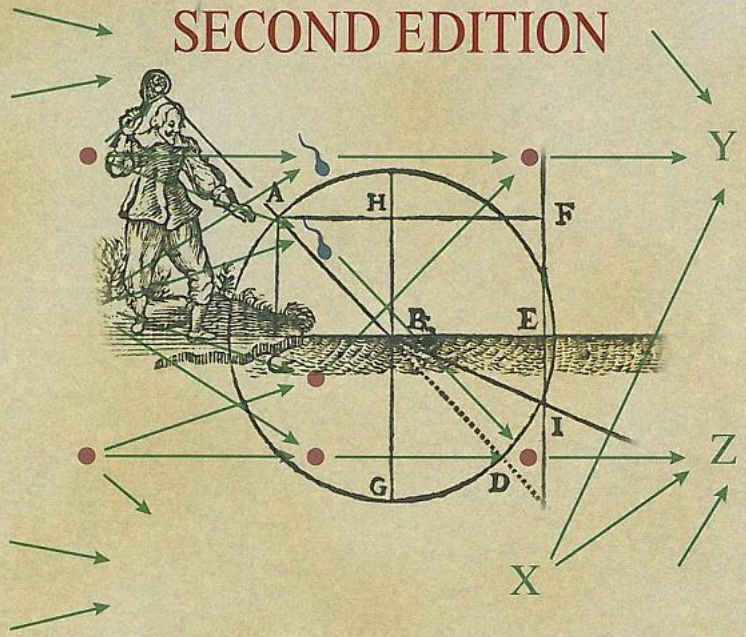
(example: Berkson bias)

Correlation without direct causality

[Hernán and Robins, 2020]

CAUSALITY

SECOND EDITION



MODELS, REASONING, AND INFERENCE

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Miguel Hernan

MIGUEL HERNAN

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Causal Inference Book

Jamie Robins and I have written a book that provides a cohesive presentation of concepts of, and methods for, causal inference. Much of this material is currently scattered across journals in several disciplines or confined to technical articles. We expect that the book will be of interest to anyone interested in causal inference, e.g., epidemiologists, statisticians, psychologists, economists, sociologists, political scientists, computer scientists... The book is divided in 3 parts of increasing difficulty: causal inference without models, causal inference with models, and causal inference from complex longitudinal data.

To cite the book, please use "Hernán MA, Robins JM (2020). Causal Inference: What If. Boca Raton: Chapman & Hall/CRC."

The components of the book can be accessed by clicking on the links below:

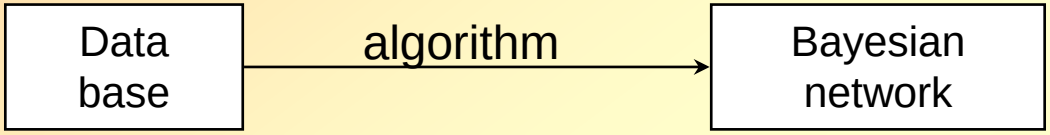
- The Causal Inference book (updated 31 July 2020)
- NHEFS data

www.hsph.harvard.edu/miguel-hernan/causal-inference-book

3.4. Building BNs

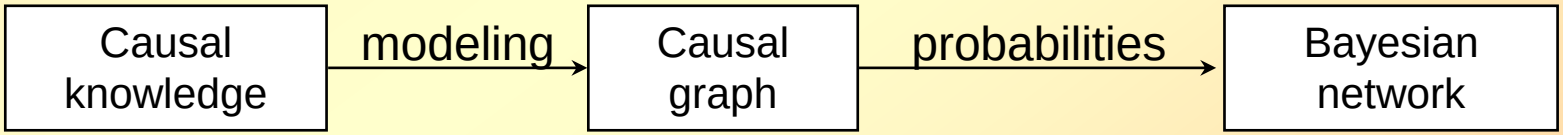
How to build a Bayesian network

- From a database



  - There are many algorithms, several new algorithms every year
  - Similar to statistical methods (logistic regression, neural nets...)

- With a human expert's help



- Hybrid methods:
  - experts $\rightarrow$ structure; database $\rightarrow$ probabilities
  - experts $\rightarrow$ initial model; new cases $\rightarrow$ refine the probabilities

3.4.1. Building BNs with causal knowledge

Where do the probabilities come from?

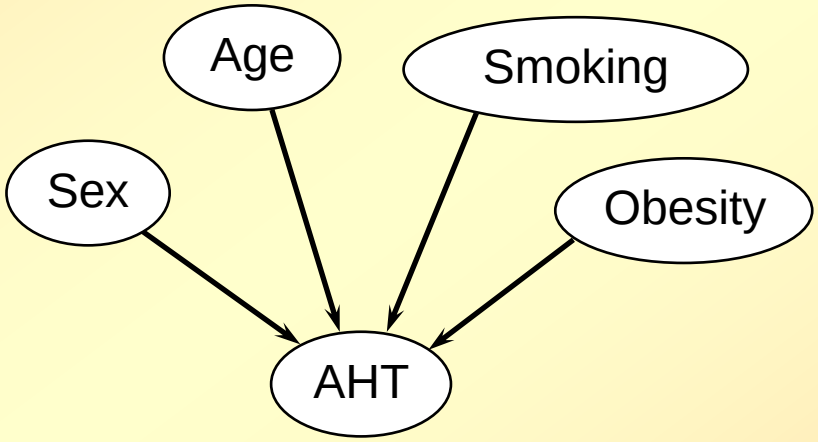
- Epidemiological studies
  - advantage: we obtain directly the parameters we need
  - difficulties: time and cost; biases (e.g. selection biases)
- Medical literature
  - advantages: reliable, relatively inexpensive
  - difficulties: few qualitative data, few direct probabilities, different criteria, population-dependent, publication biases
- Databases
  - advantages: fast, inexpensive
  - difficulties: small databases, selection biases
- Subjective estimates
  - advantage: relatively inexpensive
  - difficulties: unavailability of experts, psychological biases

3.4.1.1. Canonical models

Canonical models

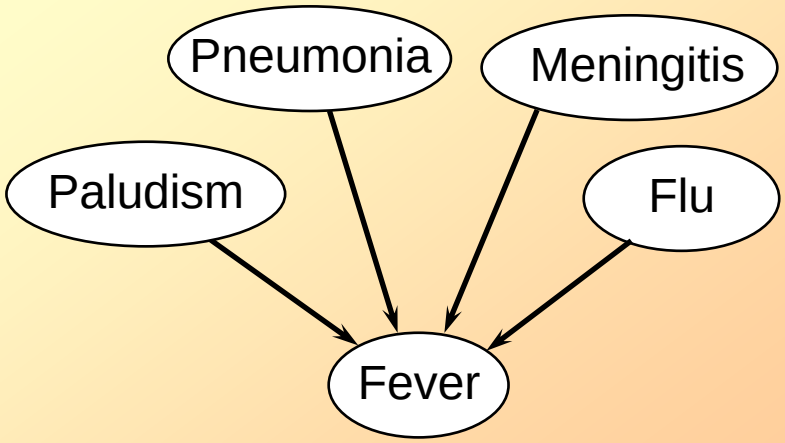
General model

- Probability table:
  $P(y \mid x_1, \ldots, x_n)$
- Factors that influence the prob. of X



Noisy OR

- Efficiency of each link:
  c_i
- Causes that can produce X



Canonical Probabilistic Models for Knowledge Engineering

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Abstract

The hardest task in knowledge engineering for probabilistic graphical models, such as Bayesian networks and influence diagrams, is obtaining their numerical parameters. Models based on acyclic directed graphs and composed of discrete variables, currently most common in practice, require for every variable a number of parameters that is exponential in the number of its parents in the graph, which makes elicitation from experts or learning from databases a daunting task. In this paper, we review the so called *canonical models*, whose main advantage is that they require much fewer parameters. We propose a general framework for them, based on three categories: deterministic models, ICI models, and simple canonical models. ICI models rely on the concept of *independence of causal influence* and can be subdivided into noisy and leaky. We then analyze the most common families of canonical models (the OR/MAX, the AND/MIN, and the noisy XOR), generalizing them and offering criteria for applying them in practice. We also briefly review temporal canonical models.

Contents

3.4.2. Learning BNs from data

Learning BNs from data

- Two possibilities of learning
  - automatic, interactive
- Two main algorithms:
  - Search-and-score
    - search
      - depart from a network with no links
      - one edit (add/remove/invert a link) in each iteration
    - score
      - use a metric (there are several metrics available) to quantify how well the model fits the data
  - PC
    - depart from a fully-connected undirected graph
    - when two variables are independent, remove the link
      - more precisely, when the correlation is not statistically significant ($p < \alpha$)
    - when two variables are conditionally indep., remove the link
    - orient the remaining links to obtain a directed graph

Hands-on exercise 2

Advantages of interactive learning

- The system proposes, the user decides
  - Very useful for tuition
  - Useful for combining data with expert knowledge
  - Useful for debugging new algorithms (workbench)
- See www.openmarkov.org/docs/tutorial.

A comparison of both methods for building BNs

- Automatic learning from databases
  - Advantage: faster (graph + probabilities)
  - Limitation: medical databases are usually incomplete
    - Missing values $\rightarrow$ problem of imputation (rarely missing at random)
    - Missing variables $\rightarrow$ spurious correlations
  - Black-box algorithm that returns non-causal models

    $\Rightarrow$ Human experts are reluctant to accept their advice
- With expert knowledge (“manual” method)
  - Only method possible when there is not a good-enough database
  - Difficulty in practice: getting the collaboration of experts
  - Building the causal graph is usually difficult
  - Obtaining the probabilities is much more difficult.

Summary: BNs vs. the naïve Bayes

- BNs can diagnose several diseases simultaneously.
- BNs do *not* assume conditional independence of findings.
- BNs are usually causal models
  - closer to doctors' reasoning: explanation of reasoning
  - probabilities are in general easier to obtain
- Three types of reasoning: abductive, deductive, inter-causal.
- They can combine data (from databases), epidemiological studies (scientific literature) and expert knowledge (doctors).

Despite these advantages,
BNs are almost unknown in medicine.
No book for medical doctors mentions them!

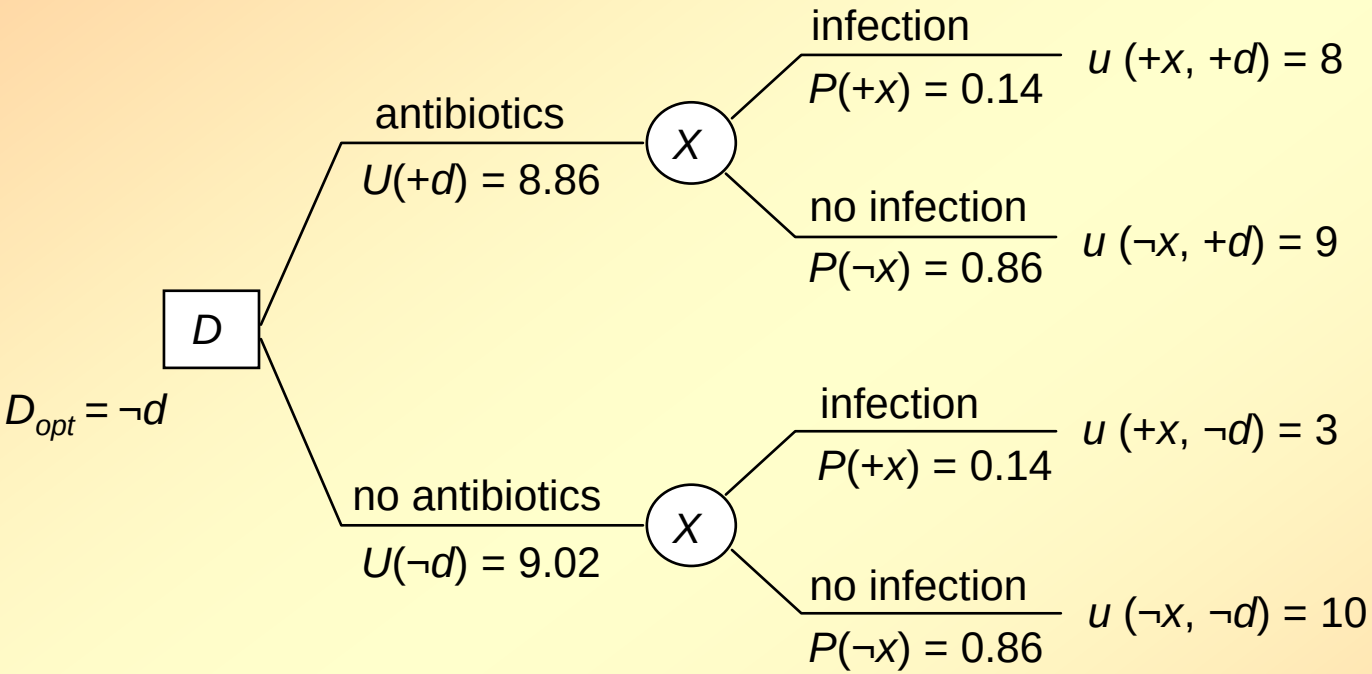
4. Unicriterion decision analysis

4.1. Introductory examples

Medical example (1)

- Suspicion of infection
  - Prior probability: 0.14
- Effectiveness:
  - No disease, no treatment: 10
  - Disease, not treated: 3
  - Disease, treated: 8
  - No disease, treatment (by mistake): 9

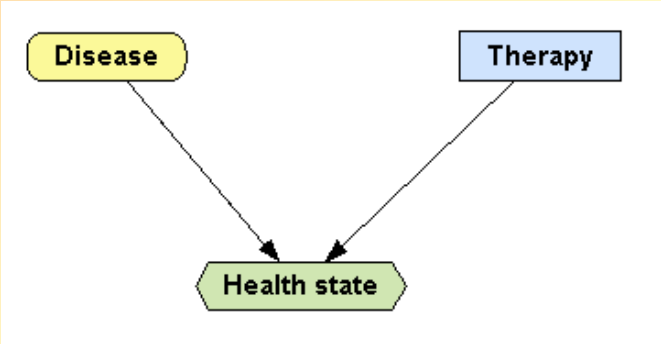
Decision tree (1)



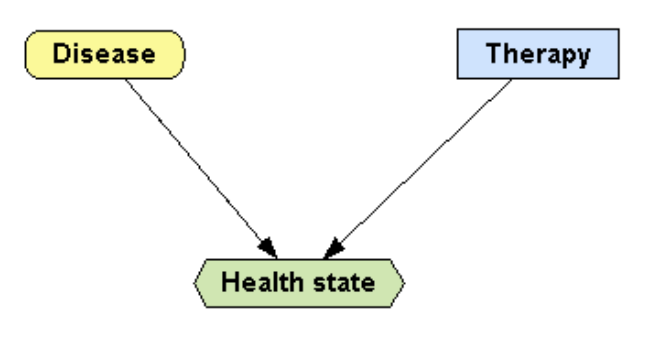
Optimal decision: $D_{opt} = \neg d \Rightarrow$ do not give antibiotics

Prognosis: $U = \max(U(+d), U(\neg d)) = \max(8.86, 9.02) = 9.02$

Influence diagram



DAN
(decision analysis network)



- Both models are identical.
- They generate the same decision tree.

Utility as a function of prevalence

$$U(d) = \sum_x u(x,d) \cdot P(x)$$

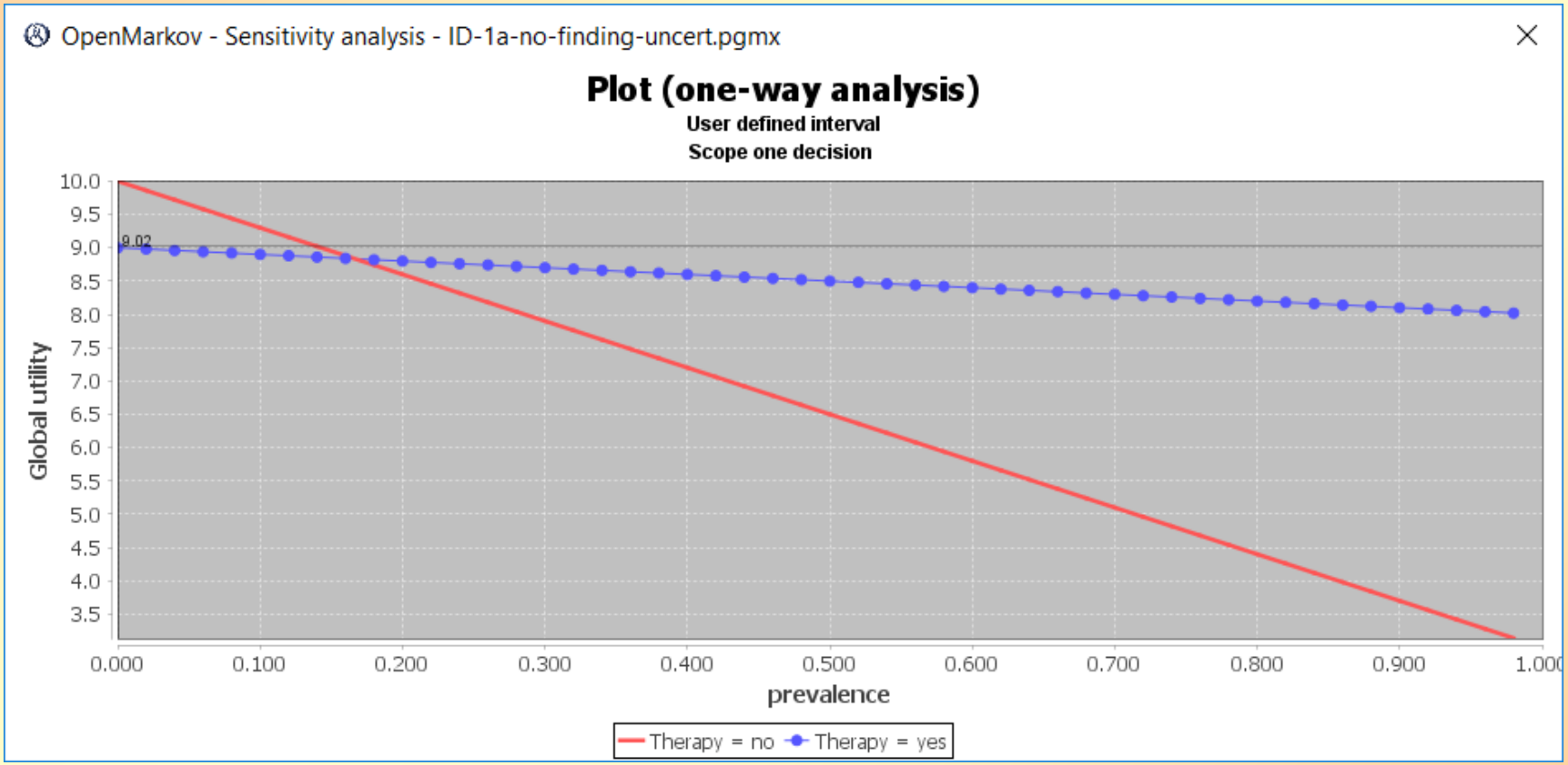
$$D_{opt} = \arg\max(U(+d), U(\neg d))$$

$$U = \max(U(+d), U(\neg d))$$

$P(+x)$	$U(+d)$	$U(\neg d)$	D_{opt}	U
0’00	9’00	10’00	$\neg d$	10’00
0’05	8’95	9’65	$\neg d$	9’79
0’14	8’86	9’02	$\neg d$	9’02
0’17	8’83	8’81	$+d$	8’83
0’40	8’60	7’20	$+d$	8’60
0’75	8’25	4’75	$+d$	8’25
1’00	8’00	3’00	$+d$	8’00

decision threshold

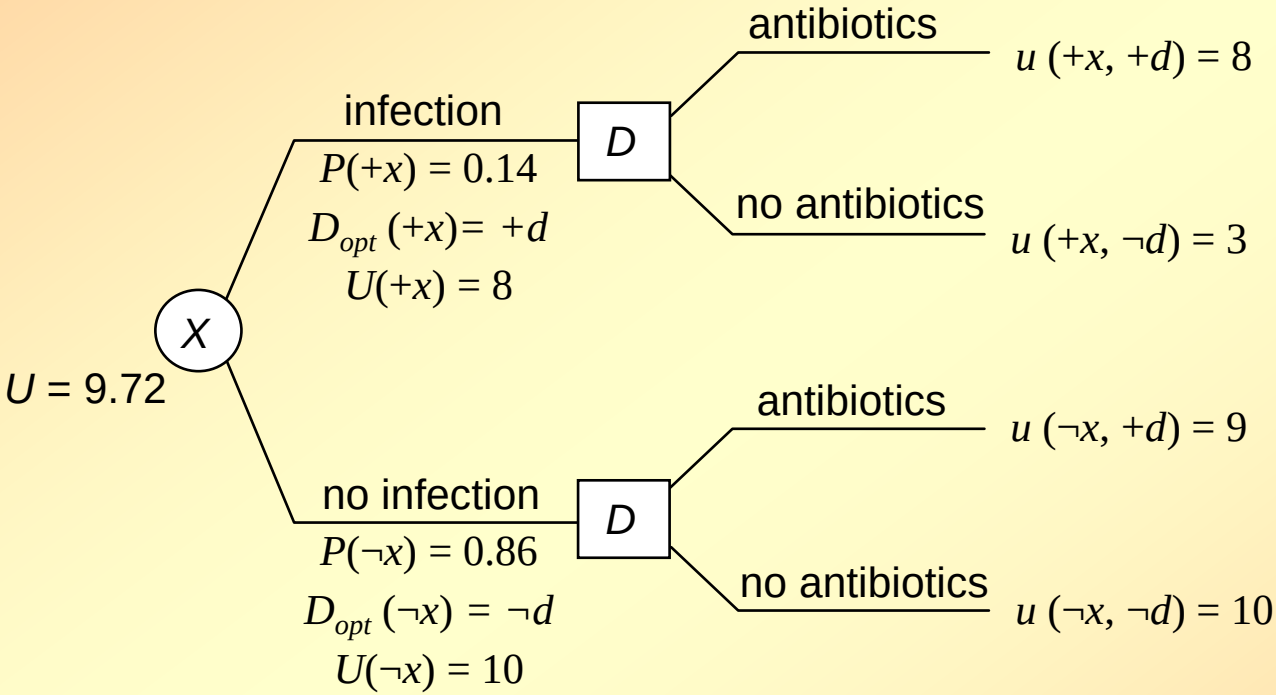
Utility as a function of prevalence



Medical example (2)

- In the previous scenario, what should we do if we knew with certainty whether the patient has the disease?
  - Question 1: What to do when infection is present?
  - Question 2: What to do when infection is absent?
- What is the average utility in this sub-population?

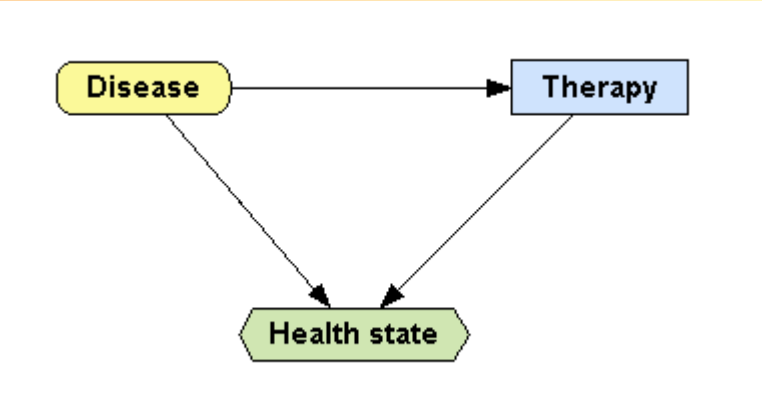
Decision tree (2)



Optimal decision: infection (+*x*) $\Rightarrow$ give antibiotics (+*d*)
no infection (¬*x*) $\Rightarrow$ do not give antibiotics (¬*d*)

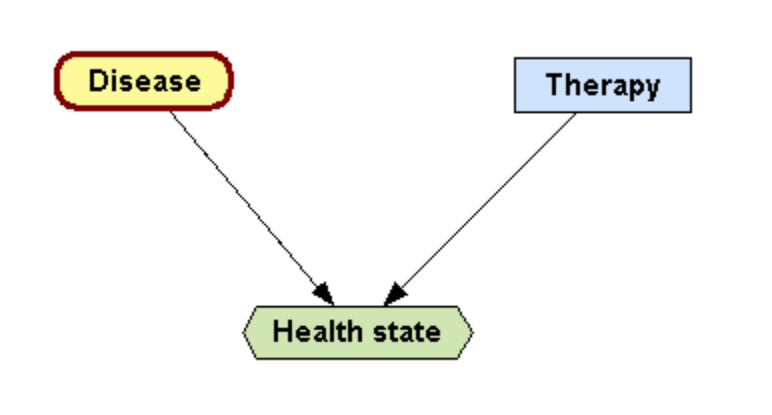
Expected utility: $U = 8 \times 0.14 + 10 \times 0.86 = 9.72$

Influence diagram



We have added an **information link**.

DAN

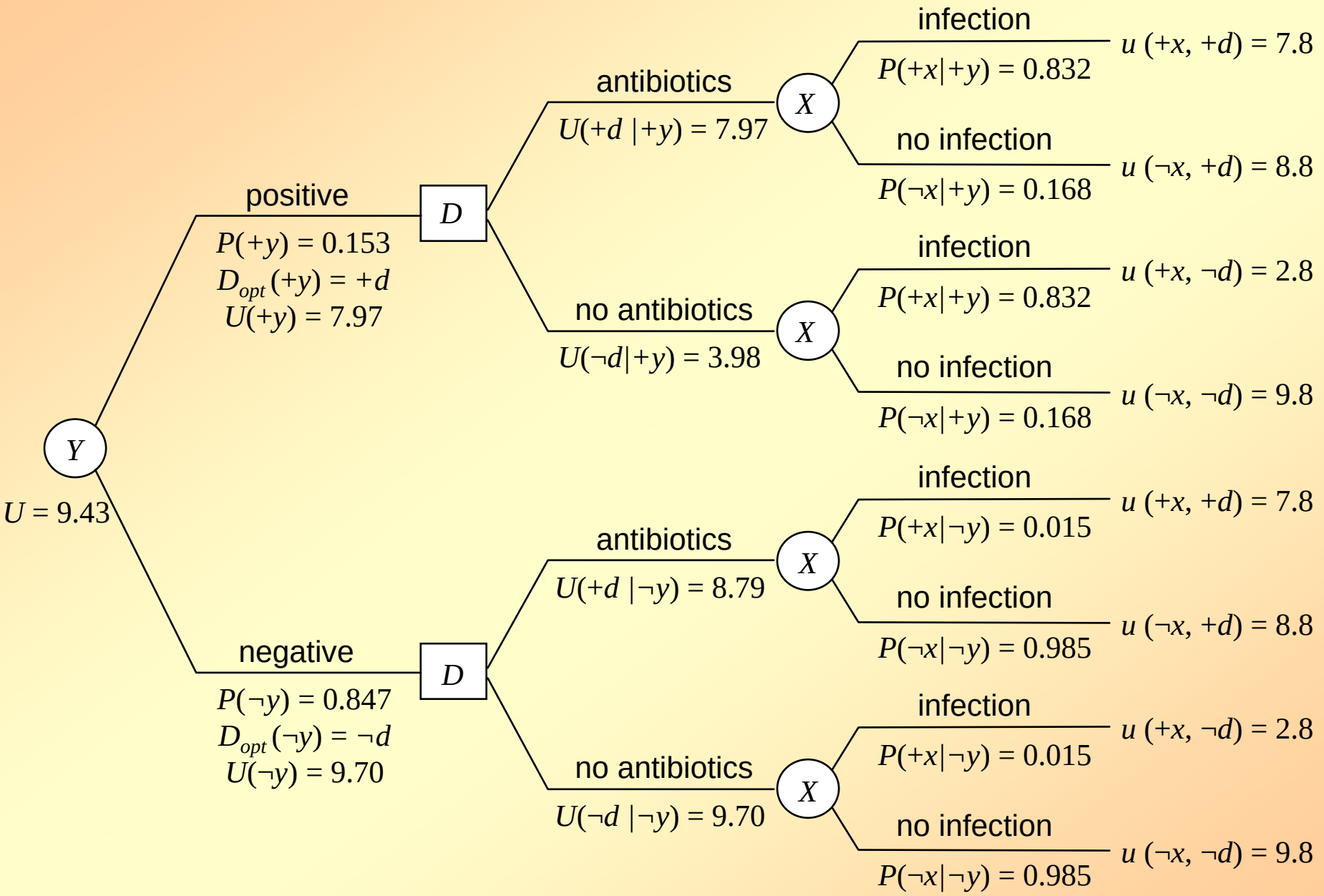


We have marked *Disease* as **always-observed**.

- Two different ways of saying that the value of *Disease* is known when making the decision *Therapy*.
- Both models are equivalent: they generate the same decision tree.

Medical example (3)

- There is a test Y
  - Sensitivity: 70%
  - Specificity: 90%
  - Cost (effectiveness decrease): 0.2
- Questions:
  - What to do when the test is positive?
  - What to do when it is negative?


Y
U = 9.43
positive
P(+y) = 0.153
D_opt(+y) = +d
U(+y) = 7.97
negative
P(¬y) = 0.847
D_opt(¬y) = ¬d
U(¬y) = 9.70
D
D
antibiotics
U(+d |+y) = 7.97
no antibiotics
U(¬d|+y) = 3.98
antibiotics
U(+d |¬y) = 8.79
no antibiotics
U(¬d |¬y) = 9.70
X
X
X
X
infection
P(+x|+y) = 0.832
u (+x, +d) = 7.8
no infection
P(¬x|+y) = 0.168
u (¬x, +d) = 8.8
infection
P(+x|+y) = 0.832
u (+x, ¬d) = 2.8
no infection
P(¬x|+y) = 0.168
u (¬x, ¬d) = 9.8
infection
P(+x|¬y) = 0.015
u (+x, +d) = 7.8
no infection
P(¬x|¬y) = 0.985
u (¬x, +d) = 8.8
infection
P(+x|¬y) = 0.015
u (+x, ¬d) = 2.8
no infection
P(¬x|¬y) = 0.985
u (¬x, ¬d) = 9.8

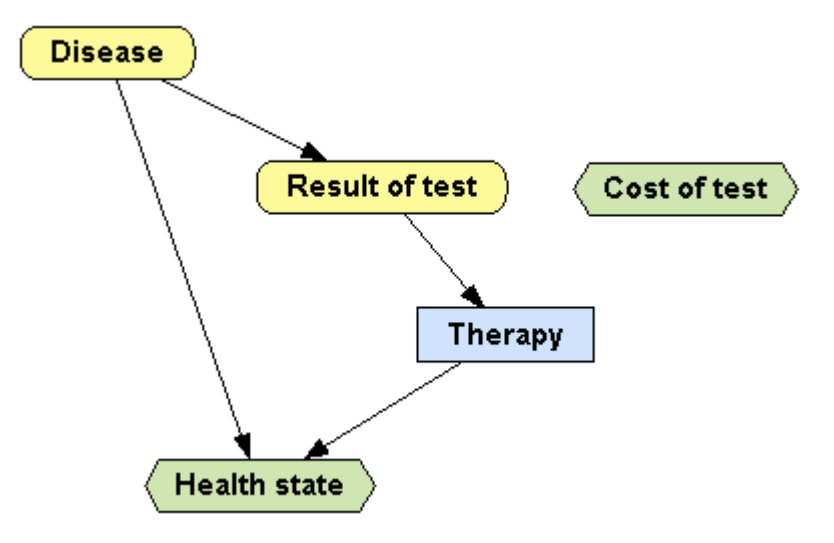
Policy and prognosis

- Policy:
  - When Y is positive: give antibiotics
  - When Y is negative: do not give antibiotics

- Prognosis
  - When Y is positive: $U(+y) = 7.97$
  - When Y is negative: $U(\neg y) = 9.70$
  - Global prognosis (average utility)

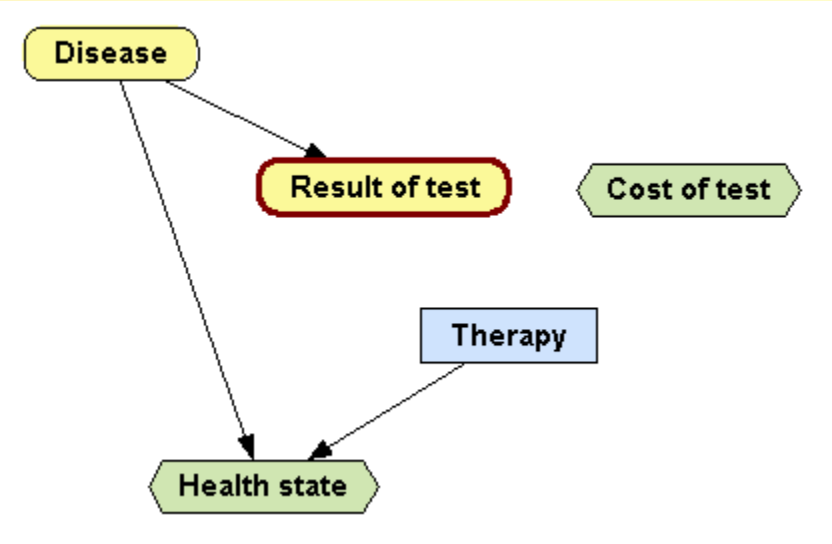
$$\begin{aligned} U_{\text{with test}} &= U(+y) \times P(+y) + U(\neg y) \times P(\neg y) \\ &= 7.97 \times 0.153 + 9.69 \times 0.847 \\ &= 9.43 \end{aligned}$$

Influence diagram



An **information link** from *Result of test* to *Therapy*

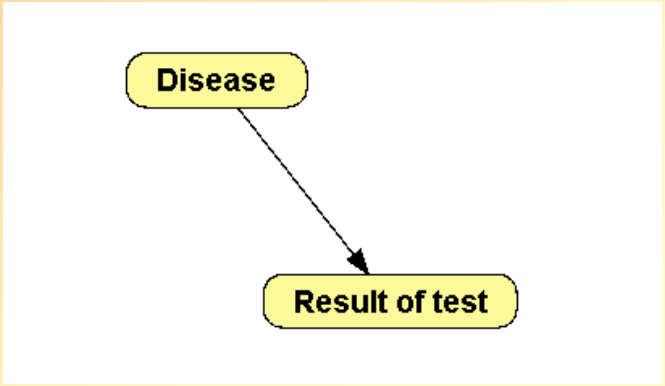
DAN



Result of test is marked as **always-observed**.

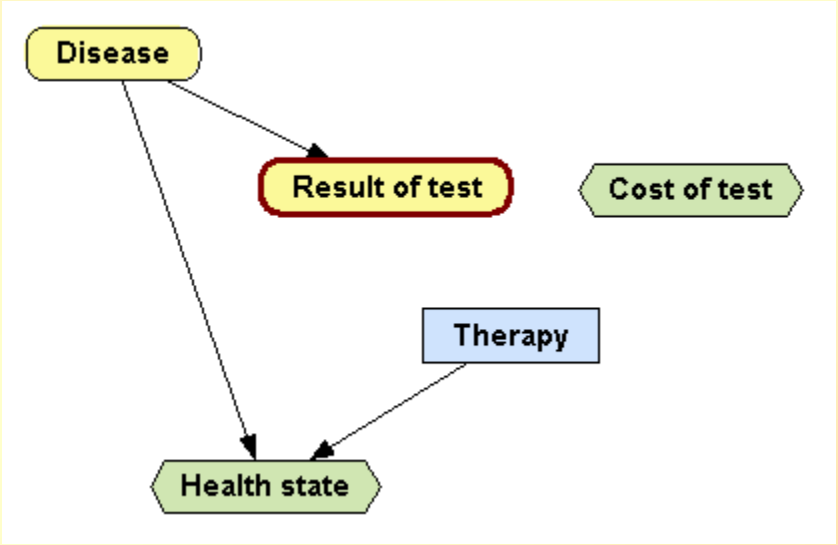
- Different ways of indicating the flow of information.
- Both models generate the same decision tree.

Bayesian networks



- Only chance nodes
- Used for diagnosis
- Can be learned from data

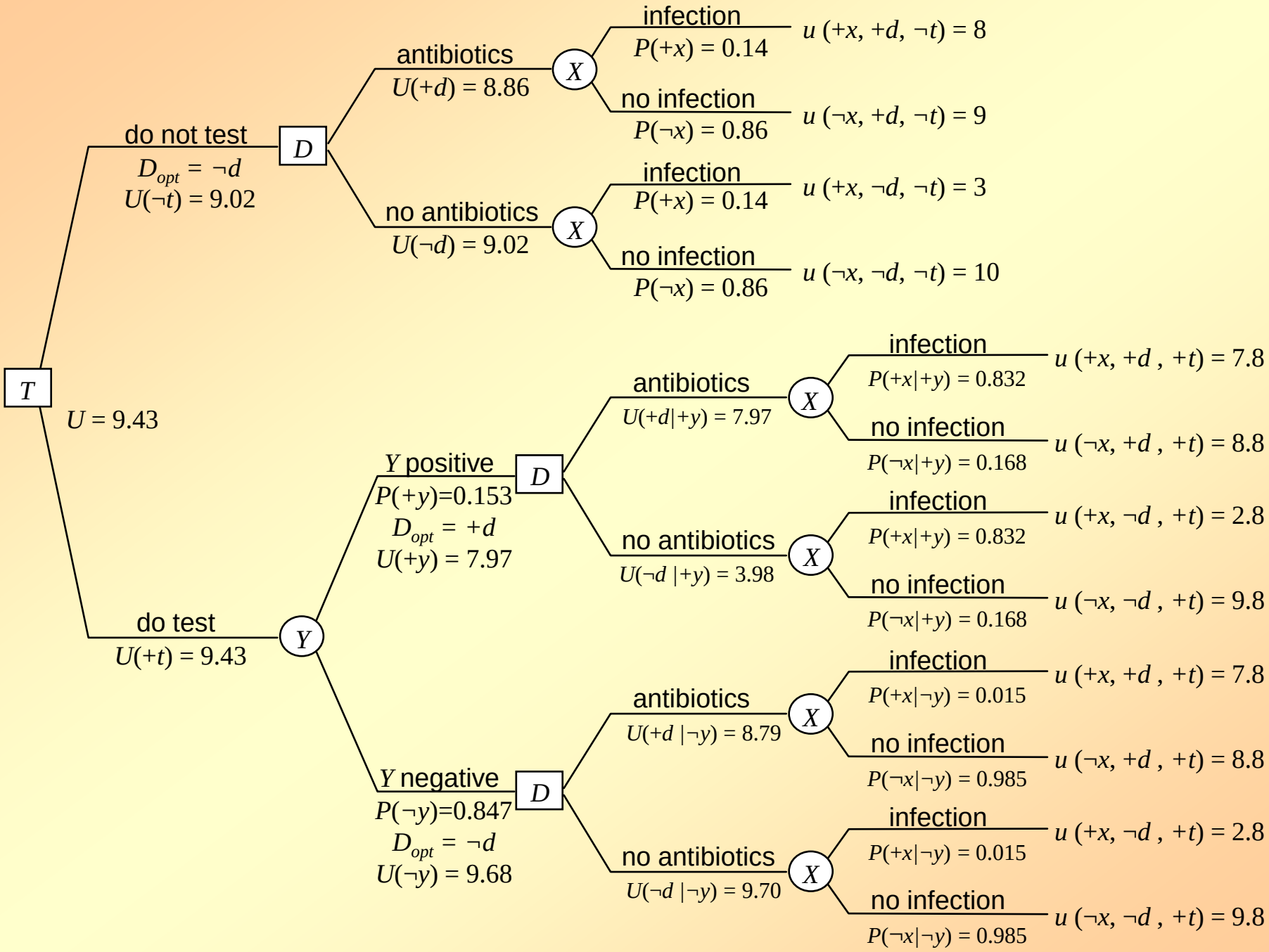
IDs / DANs



- Three types of nodes:
  chance, decision, utility
- Used for decision analysis
- Require causal knowledge

Medical example (4): deciding about a test

- Test Y
  - Advantage: gives information
  - Disadvantage: has a cost
- Is it worth doing the test?
- Three possible policies:
  1. Give the therapy to all patients, preventively
  2. Never apply the therapy
  3. Do test Y; apply the therapy only when it is positive


T
U = 9.43
do not test
D_opt = ¬d
U(¬t) = 9.02
D
antibiotics
U(+d) = 8.86
X
infection
P(+x) = 0.14
u (+x, +d, ¬t) = 8
no infection
P(¬x) = 0.86
u (¬x, +d, ¬t) = 9
no antibiotics
U(¬d) = 9.02
X
infection
P(+x) = 0.14
u (+x, ¬d, ¬t) = 3
no infection
P(¬x) = 0.86
u (¬x, ¬d, ¬t) = 10
do test
U(+t) = 9.43
Y
Y positive
P(+y)=0.153
D_opt = +d
U(+y) = 7.97
D
antibiotics
U(+d|+y) = 7.97
X
infection
P(+x|+y) = 0.832
u (+x, +d , +t) = 7.8
no infection
P(¬x|+y) = 0.168
u (¬x, +d , +t) = 8.8
no antibiotics
U(¬d |+y) = 3.98
X
infection
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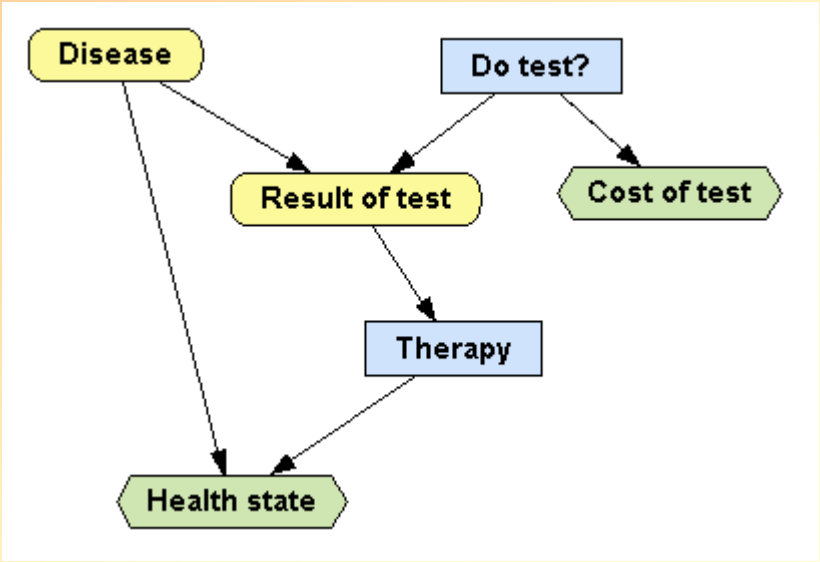
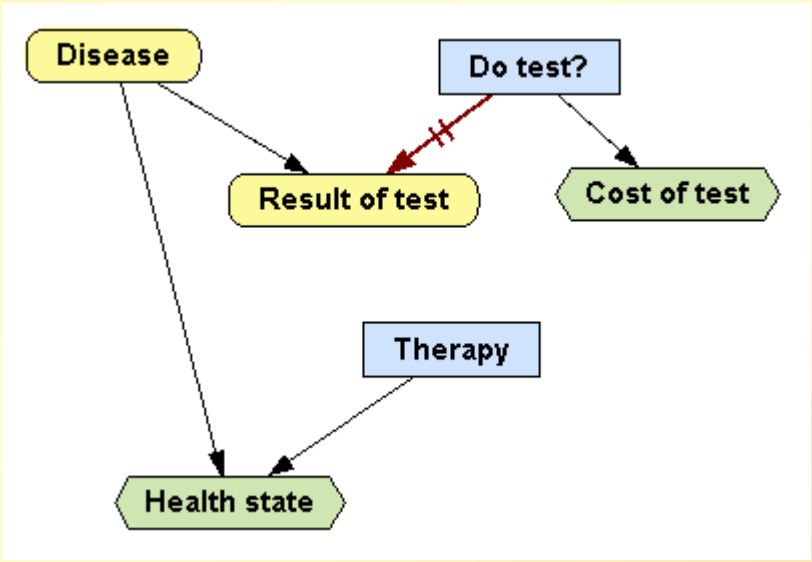
no infection
P(¬x|+y) = 0.168
u (¬x, ¬d , +t) = 9.8
Y negative
P(¬y)=0.847
D_opt = ¬d
U(¬y) = 9.68
D
antibiotics
U(+d |¬y) = 8.79
X
infection
P(+x|¬y) = 0.015
u (+x, +d , +t) = 7.8
no infection
P(¬x|¬y) = 0.985
u (¬x, +d , +t) = 8.8
no antibiotics
U(¬d |¬y) = 9.70
X
infection
P(+x|¬y) = 0.015
u (+x, ¬d , +t) = 2.8
no infection
P(¬x|¬y) = 0.985
u (¬x, ¬d , +t) = 9.8

Influence diagram



An **information link**.
Total ordering of the decisions

DAN



Restrictions. **Revelation link**.
The decisions are not ordered.

- Different ways of indicating the flow of information.
- The decision trees are different but <u>equivalent</u>:
  the same probabilities, utilities, and policies.

Conditional prob. for *Result of test*

in the ID

Node Potential: Result of test

Relation Type: Table Reor

Do test?	no	no	yes	yes
Disease	absent	present	absent	present
positive	0	0	0.03	0.91
negative	0	0	0.97	0.09
not done	1	1	0	0

- dummy value:
  test not done

in the DAN

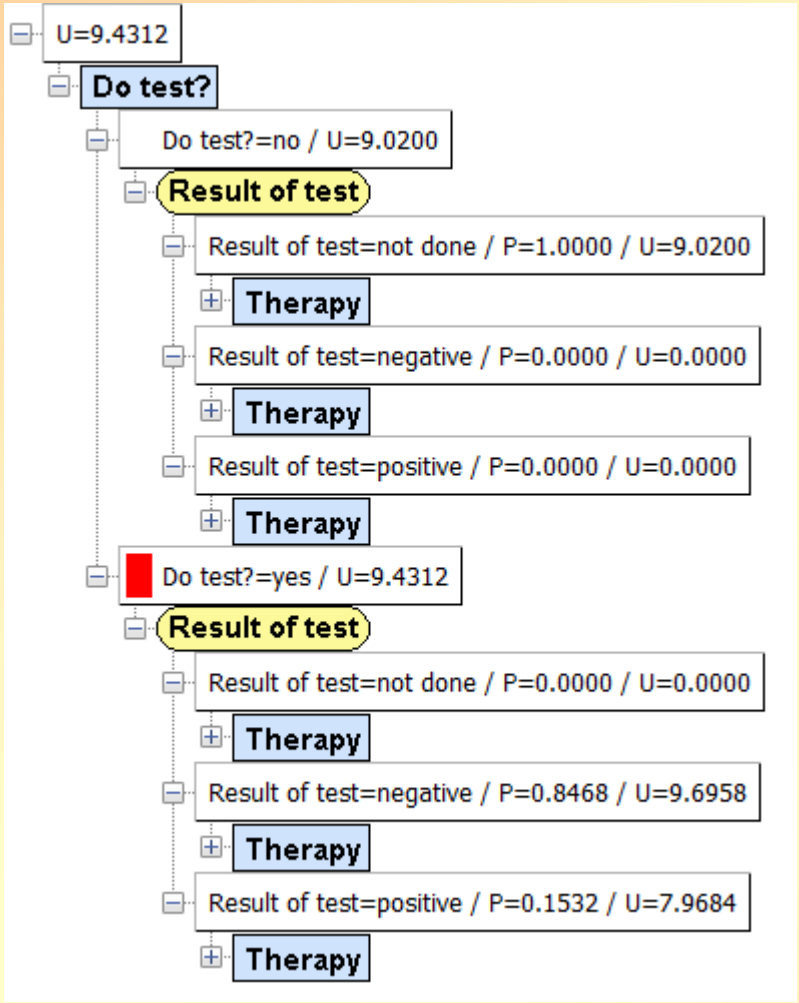
Node Potential: Result of test

Relation Type: Table Reor

Do test?	no	no	yes	yes
Disease	absent	present	absent	present
positive	0	0	0.03	0.91
negative	0	0	0.97	0.09

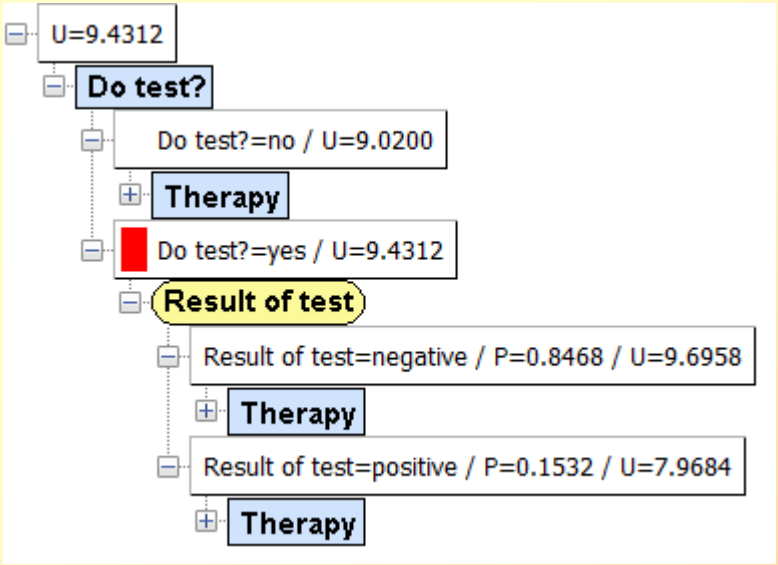
- restrictions
- no dummy value

Decision tree generated by the ID



symmetric

Decision tree generated by the DAN



asymmetric

Hands-on exercise 3

Exercise: Optimal stratety for two tests

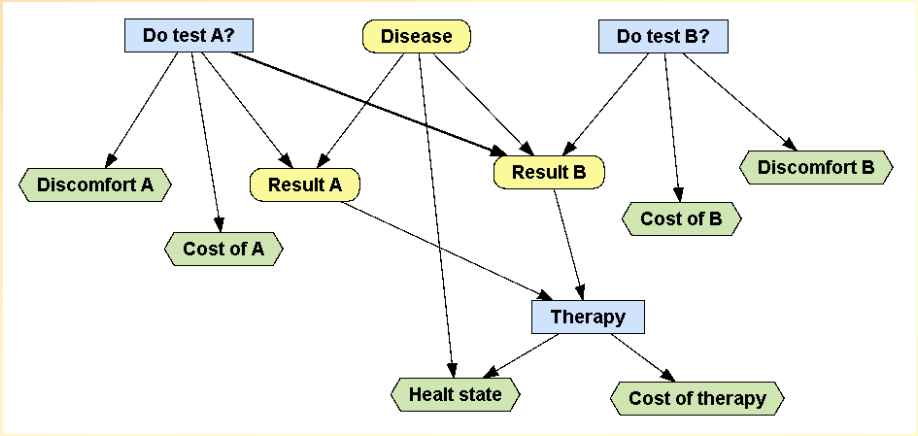
Test	sensitivity	specificity	discomfort
A	0.60	0.92	0.0003 QALY
B	0.80	0.91	0.0001 QALY

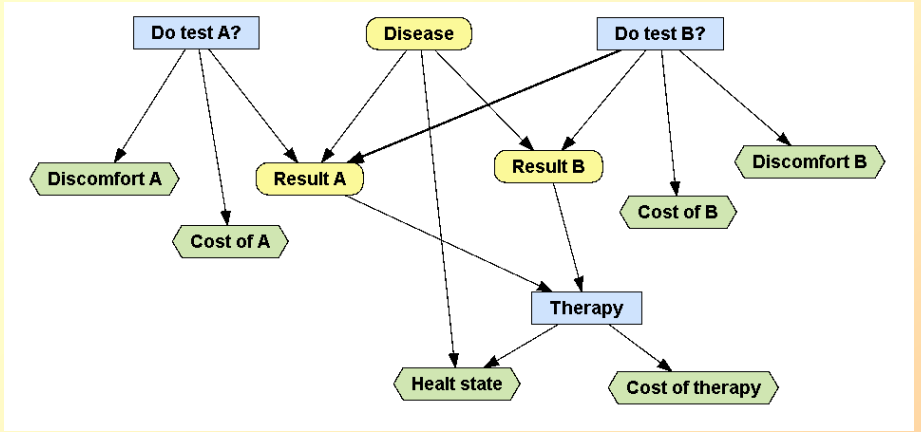
Disease →	absent	present
therapy	38 QALY	30 QALY
no therapy	40 QALY	20 QALY

- Question: What is the most effective strategy?

Solution with influence diagrams

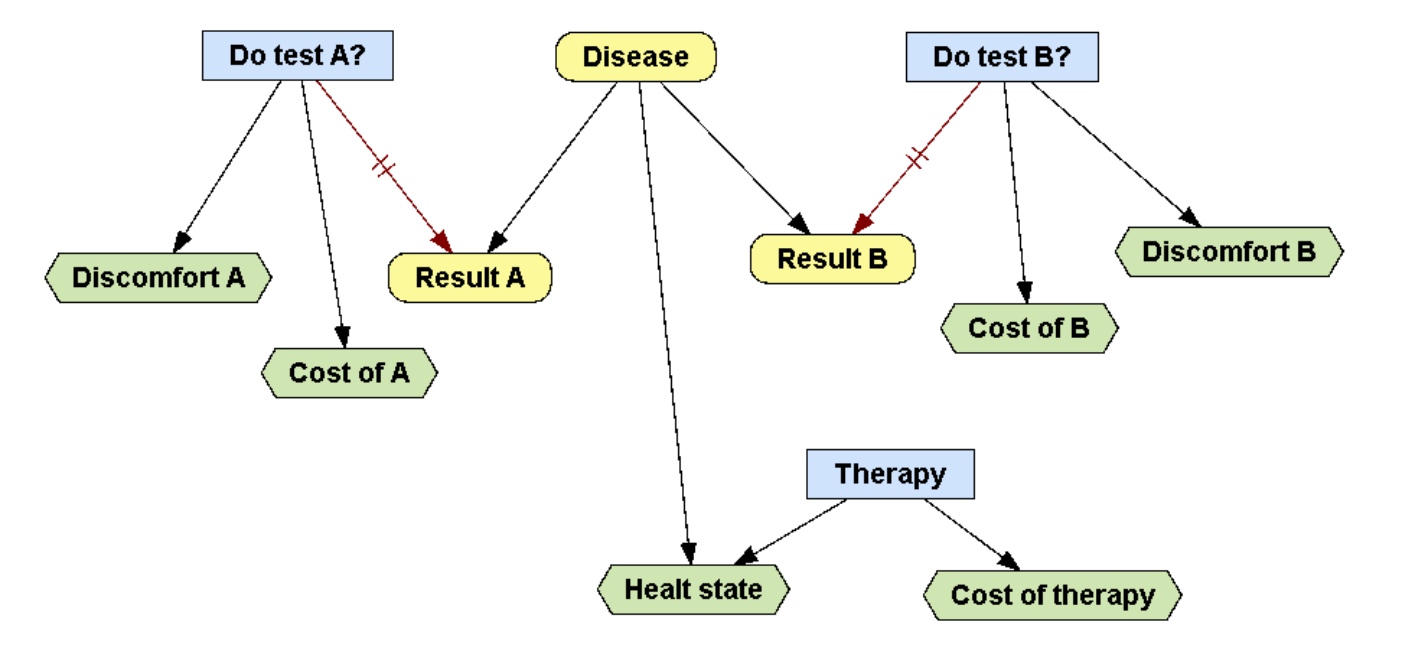
- IDs require a total ordering of the decisions
- It is not possible to represent this problem with one ID
- Trick: use two influence diagrams





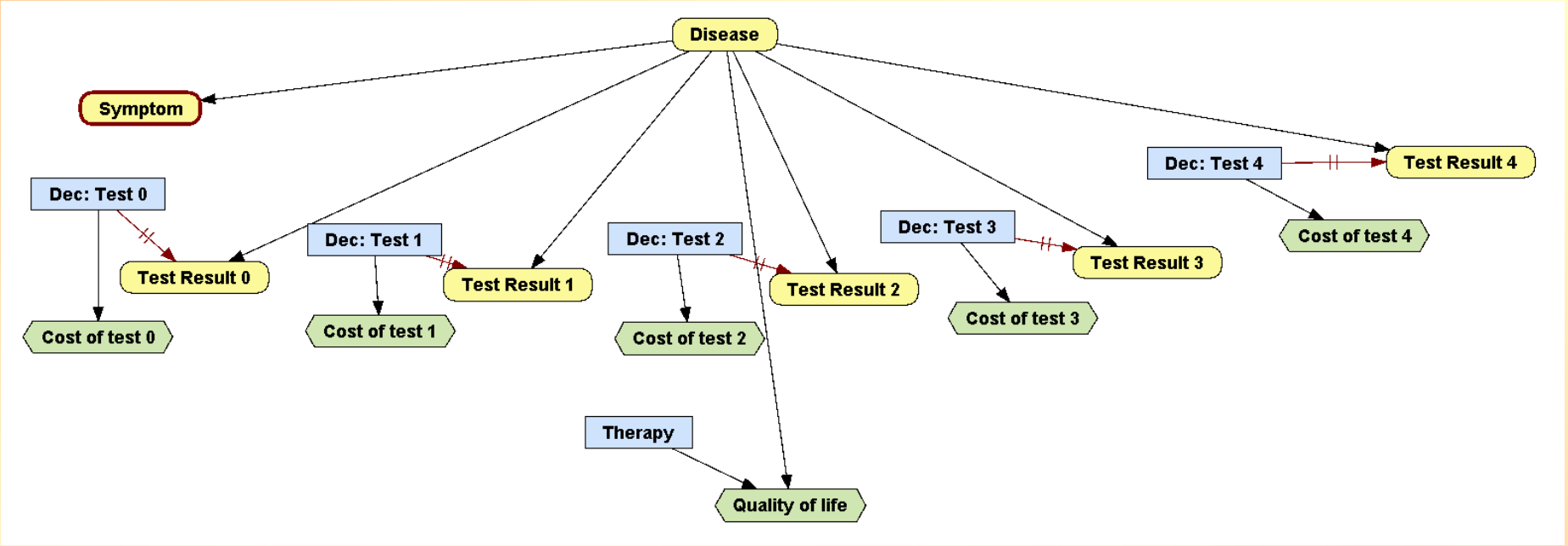
- We choose the order (the ID) with the higher expected utility.
- This trick does not work for more than two tests.

Solution with a DAN



- Advantages wrt IDs
  - one network is sufficient
  - no dummy states, such as “test not done”
  - can accommodate any number of tests

The n-test problem



- Computationally hard: $n!$ possible orderings of the tests.
- We have developed an any-space algorithm for this problem
- and a fast algorithm (9 minutes for the 7-test problem).
- It is possible to develop even more efficient algorithms.

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Decision analysis networks

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ABSTRACT

This paper presents decision analysis networks (DANs) as a new type of probabilistic graphical model. Like influence diagrams (IDs), DANs are much more compact and easier to build than decision trees and can represent conditional independencies. In fact, for every ID there is an equivalent symmetric DAN, but DANs can also represent asymmetric problems involving partial orderings of the decisions (order asymmetry), restrictions between the values of the variables (domain asymmetry), and conditional observability (information asymmetry). Symmetric DANs can be evaluated with the same algorithms as IDs. Every asymmetric DAN can be evaluated by converting it into an equivalent decision tree or, much more efficiently, by decomposing it into a tree of symmetric DANs. Given that DANs can solve symmetric problems as easily and as efficiently as IDs, and are more appropriate for asymmetric problems—which include virtually all real-world problems—DANs might replace IDs as the standard type of probabilistic graphical model for decision support and decision analysis. We also argue that DANs compare favorably with other formalisms proposed for asymmetric decision problems. In practice, DANs can be built and evaluated with OpenMarkov, a Java open-source package for probabilistic graphical models.

1. Introduction

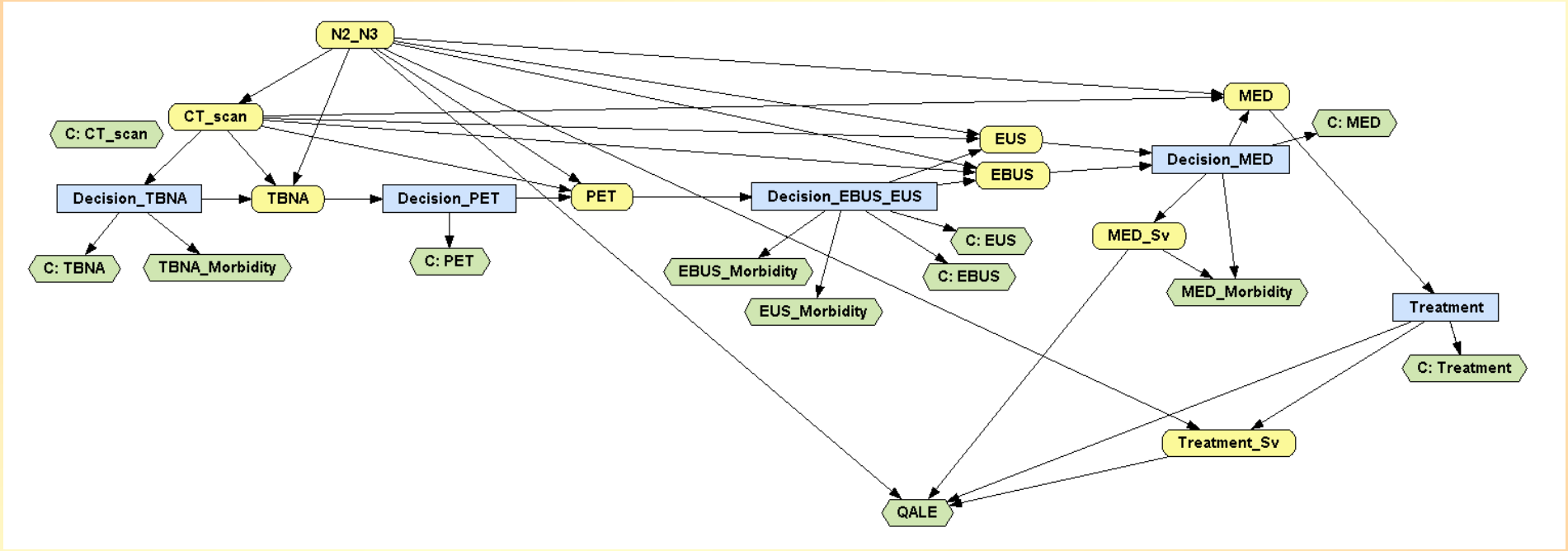
The two formalisms most widely used for the representation and analysis of decision problems are decision trees (DTs) [31] and influence diagrams (IDs) [15]. DTs have the advantage of almost absolute flexibility, but also have three drawbacks: their size grows exponentially with the number of variables, they cannot represent conditional independencies, and they

DANs vs. IDs

- DANs can replace IDs as the standard decision analysis tool (in AI, MDM, operations research…) because:
  - For every ID there is an equivalent symmetric DAN
    - but for many DANs there is no equivalent ID
  - Virtually all real-world problems are asymmetric.
  - There many problems that cannot be modeled with IDs.
  - Even if a problem can be modeled with an ID, a DAN is usually better because it does not need dummy states.

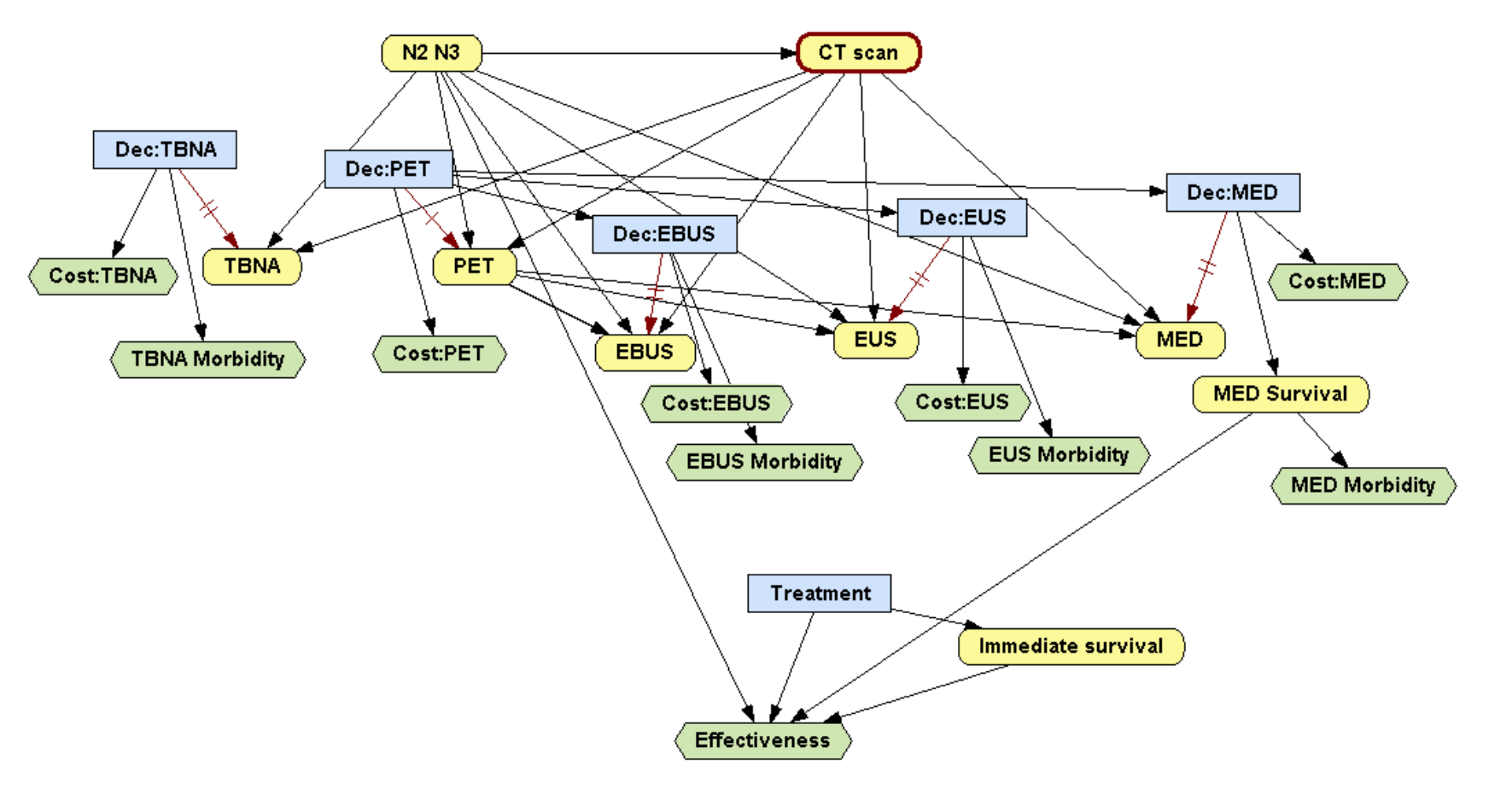
4.2. Examples of decision models for real-world problems

Mediastinet, an ID for lung cancer



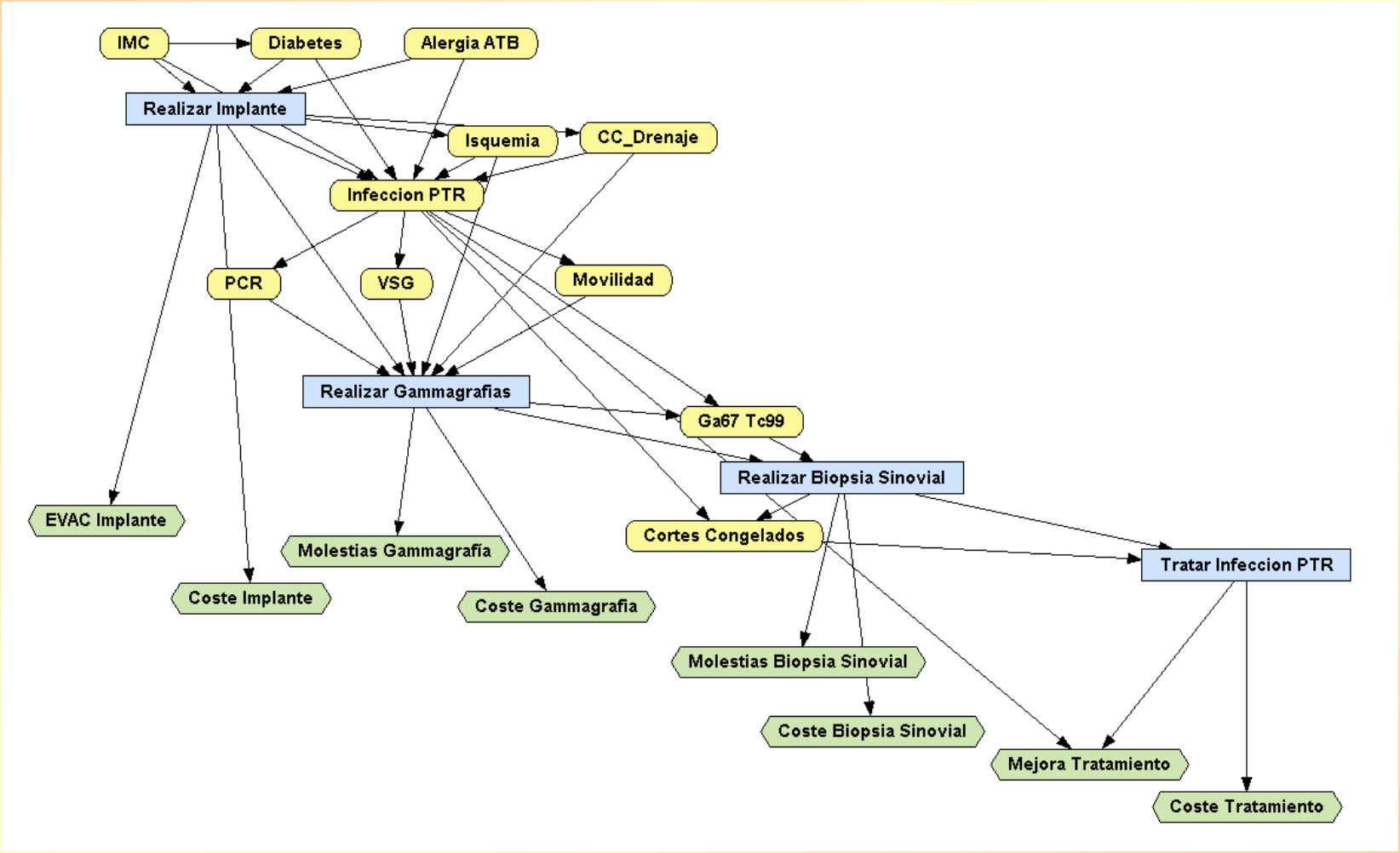
Equivalent to a decision tree containing ~10^4 branches.

Mediastinet (DAN version)



Decisions are partially ordered.

Arthronet, an ID for total knee arthroplasty



Equivalent to a decision tree containing ~10^4 branches.

4.3. Advantages and limitations of influence diagrams

Advantages of influence diagrams (1/3)

- IDs are more compact than decision trees
  - An ID having *n* binary nodes ~ a DT having 2^n branches
- IDs transform automatically into decision trees
  - ... but the reverse is not true (no general algorithm)
  - If you build a decision tree, you only have a decision tree.
  - If you build an ID, you have both.
- IDs are much easier to build than decision trees
  - IDs use direct probabilities (prevalence, sensitivity, specificity...) and costs (mortality, morbidity, economic cost...)
  - ID can use canonical models (noisy OR, noisy AND, etc.)
  - Each parameter appears only once in the ID
    - in many cases it is not necessary to have parametric variables
  - IDs can have several value nodes: more clarity, separate criteria

Advantages of influence diagrams (2/3)

- No pre-calculation of probabilities is required
- Having all the information, no debugging is usually needed
  - On the contrary, "all trees have bugs" (Primer on MDA, in *MDM* journal)
- IDs are much easier to modify than decision trees
  - Refine the model with new decisions and chance variables
  - Structural sensitivity analysis
  - Can adapt to different regional settings
  - Can adapt to patient's medical characteristics and preferences
- Explicit representation of causality
  - a link indicates causal influence
  - the absence of a link means "no causal influence" (hypothesis)

Advantages of influence diagrams (3/3)

- Two possibilities of evaluation:
  1. expansion of an equivalent decision tree
     - exponential complexity (time and space)
     - equivalent to the brute-force method for Bayesian networks
     - many problems can not be solved with this method
  2. operations on the ID (recursive reduction of the ID)
     - direct manipulation of the graph and/or potentials of the ID
     - similar to the best algorithms for Bayesian networks
     - canonical models and the separation of utility nodes can lead to more efficient evaluations
- More possibilities of explanation of reasoning
  - computation of posterior probabilities on the ID (as if it were a BN)
  - value of information (EVPI and other measures) can be computed easily
  - other methods from Bayesian networks and qualitative prob. networks.

  These methods can be used to debug/refine IDs.

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The Influence of Influence Diagrams on Artificial Intelligence

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Howard and Matheson's article "Influence Diagrams" has had a substantial impact on research in artificial intelligence (AI). In this perspective, I briefly discuss the importance of influence diagrams as a model for decision making under uncertainty in the AI research community; but I also identify some of the less direct, but no less important, influences this work has had on the field.

Key words: influence diagrams; decision theory; artificial intelligence; value of information; graphical models; perspective, the focus on graphical modeling research
History: Received on November 14, 2005. Accepted by Eric Horvitz on November 23, 2005, without revision.

Howard and Matheson's (1984/2005) "Influence Diagrams" has had a profound impact on developments in artificial intelligence. Some of these influences have been quite direct; others are more indirect, but in many ways, more substantial. The paper itself is representative of developments that had been

vision (Binford and Levitt 2003), dialog management, user interface design, multiagent systems, and game theory (Koller and Milch 2003), to name but a few.

Another reasonably direct impact of "Influence Diagrams" derives from its role in the development of graphical models for probabilistic modeling and

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informs

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The Influence of Influence Diagrams in Medicine

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Although influence diagrams have used medical examples almost from their inception, that graphical representation of decision problems has disseminated surprisingly slowly in the medical literature and among clinicians performing decision analyses. Clinicians appear to prefer decision trees as their primary modeling metaphor. This perspective examines the use of influence diagrams in medicine and offers explanations and suggestions for accelerating their dissemination.

Key words: decision analysis; influence diagrams; clinical decision making; medicine
History: Received December 12, 2005. Accepted by Eric Horvitz on January 5, 2006, after 1 revision.

Introduction

Two decades after Howard's landmark paper (Howard and Matheson 1984/2005) that introduced the concept of the influence diagram and three decades since Miller's initial report (Miller et al. 1976), *Decision Analysis* reproduced that paper in 2005 and solicited a set of commentaries. This paper

modeling paradigm slowly spread from Stanford, both with courses offered at meetings of the Society for Medical Decision Making (Society for Medical Decision Making 2005) and with the development of software that could conveniently capture and evaluate such models.

IDs in the literature on MDM (1/3)

- Books that mention decision trees but do not mention IDs
  - Weinstein, Fineberg. *Clinical Decision Making*. 1980.
  - Sloan (ed.). *Valuing Health Care*. 1995.
  - Gold et al. *Cost-Effectiveness in Health and Medicine*. 1996.
  - Sackett et al. *Evidence-Based Medicine*. 1997 (and three other books on EBM).
  - Petitti. *Meta-Analysis, Decision Analysis and CEA*. 2nd ed., 2000.
  - Drummond, McGuire (eds.). *Economic Eval. in Health Care Programs*. 2001.
  - Levin and McEwan. *Cost-Effectiveness Analysis*. 2nd ed., 2001.
  - Parmigiani. *Modelling in Medical Decision* Making. 2002.
  - Haddix et al. *Prevention Effectiveness*. 2nd ed., 2003.
  - Fox-Rushby and Cairns. *Economic Evaluation.* 2005.
  - Briggs et al. *Decision Modelling for Health Economic Evaluation*, 2006.
  - Alemi and Gustafson. *Decision Analysis for Healthcare Managers*, 2006.
  - Arnold. *Pharmacoeconomics: From Theory to Practice*. 2009.
  - Kassirer et al. *Learning Clinical Reasoning*. 2nd ed., 2010.
  - Mushlin and Greene. *Decision Making in Medicine*. 3rd ed., 2010.

(cont'd)

IDs in the literature on MDM (2/3)

- Books that mention decision trees but do not mention IDs (cont.)
  - Gray et al. *Applied Methods of CEA in Health Care*, 2011.
  - Alfaro-LeFevre. *Critical Thinking, Clinical Reasoning…* 5th ed., 2013.
  - Morris et al. *Economic Analysis in Healthcare*. 2nd ed., 2012.
  - Rascati. *Essentials of Pharmacoeconomics*. 2nd ed., 2013.
  - Sox et al. *Medical Decision Making*. Latest ed., 2013.
  - Hunink et al. *Decision Making in Health and Medicine*. 2nd ed., 2014.
  - Drummond et al. *Methods for the Economic Evaluation of…* 4th ed. 2015.
  - Edlin et al. *Cost Effectiveness Modelling for HTA…* 2015.
  - Neumann et al. *Cost-Effectiveness in Health and Medicine*. 2016
  - Caro et al. *Discrete Event Simulation for HTA*. 2016

- One book that mentioned IDs
  - Muennig. *Designing and Conducting Cost-Effectiveness Analyses in Medicine and Health Care*. 2002, page 242:

    "An influence diagram (also known as a tornado diagram) ..."

    The 2nd edition (2007) and the 3rd (2016) do not mention them.

IDs in the literature on MDM (3/3)

- Three books that describe IDs
  - Chapman and Sonnenberg (eds.). *Decision Making in Health Care*. 2000 (5 pages out of 421, in a chapter by Mark Roberts)
  - Schwartz and Bergus. *Medical Decision Making. A Physician's Guide*. 2008. (2 pages out of 230)
  - Kattan. *Encyclopedia of Medical Decision Making*. 2009 (4 pages out of 1200+).
- Summary of the informal survey of books on MDM and EBM
  - 26 books published after 1984
  - All of them explain DTs but only 3 describe IDs, very briefly.
- Some books on medical informatics mention IDs:
  - Shortliffe and Cimino. *Biomedical Informatics*. 4th ed., 2013 (2.5 pages out of 991).
  - Kalet. *Principles of Biomedical Informatics*. 2nd ed., 2013 (3 pages out of 708).
- Why are IDs so little known in health sciences after 35+ years?

Limitations of IDs

1. The “reasoning” of an ID is not easy to understand
2. The evaluation returns large policy tables
3. IDs can only model symmetric problems
   - IDs require a total ordering of the decisions
   - IDs cannot represent incompatibilities between values
     - Non-standard versions of IDs partially solve this problem, but none of the alternatives was completely satisfactory.
4. Algorithms could only evaluate unicriterion IDs
   - They could not perform cost-effectiveness analysis
5. Temporal reasoning was not possible with IDs
   - Dynamic IDs are computationally unfeasible.

Solutions we have proposed

1. Explanation in influence diagrams
   - showing the posterior probabilities and expected values
   - introduction of evidence
   - hypothetical reasoning (what if) by means of imposed policies
2. Synthesizing the optimal intervention
   - in the form of a compact tree
3. Decision analysis networks (DANs)
   - an alternative to IDs for asymmetric decision problems.
4. Cost-effectiveness analysis with IDs
5. Markov influence diagrams
   - including cost-effectiveness analysis

} after the break

Break: 20 minutes

5. Cost-effectiveness analysis

5.1. Deterministic CEA

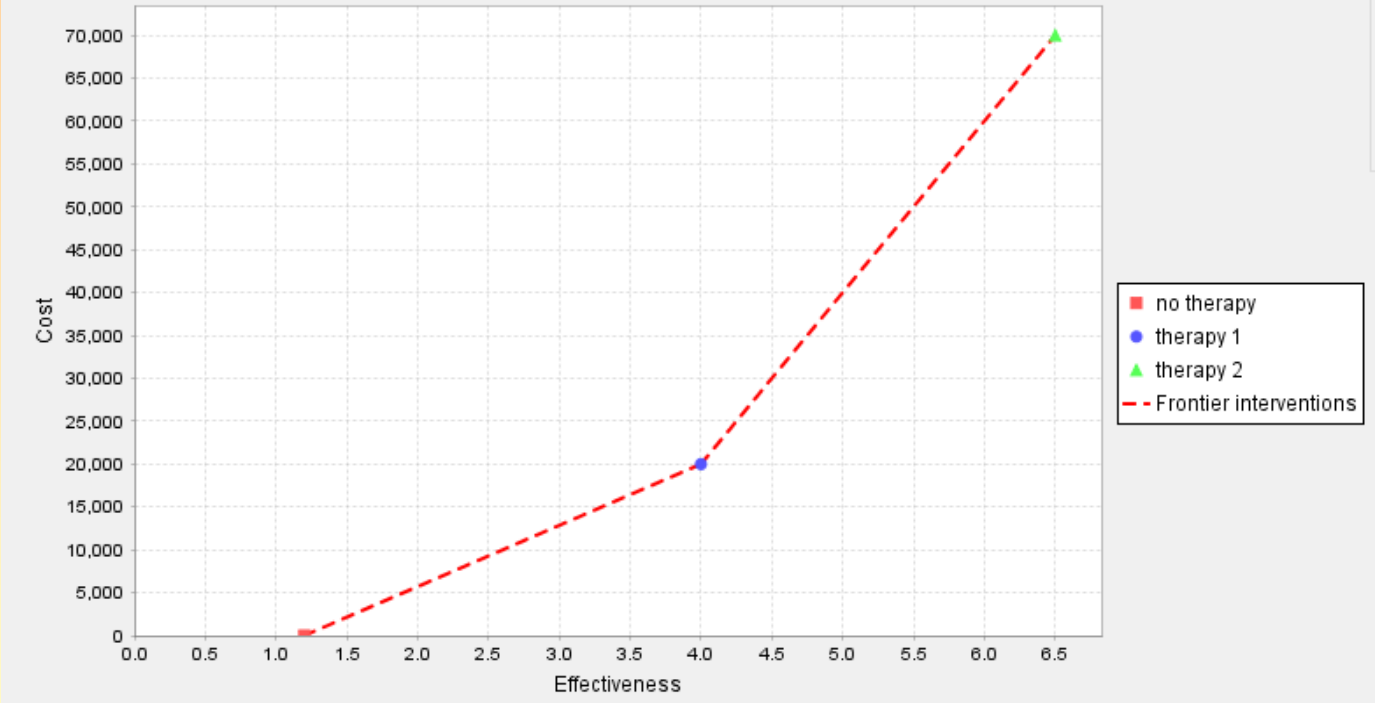
An example with costs and effectiveness

- Two therapies
  - Therapy 1: cost = € 20,000
  - Therapy 2: cost = € 70,000
  - Effectiveness (QALY)

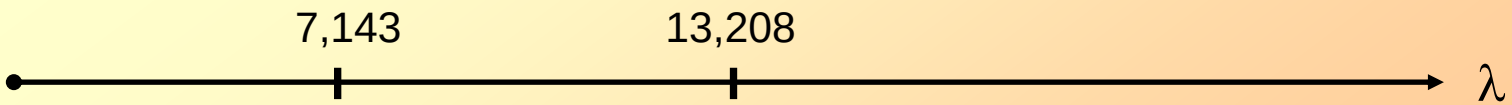
	No therapy	Therapy 1	Therapy 2
Disease present	1.2	4.0	6.5
Disease absent	10	9.9	9.3

- Questions:
  - Which therapy to apply when the disease is present
  - Which therapy to apply when the disease is absent
- The answer may depend on λ, the willingness to pay (WTP)

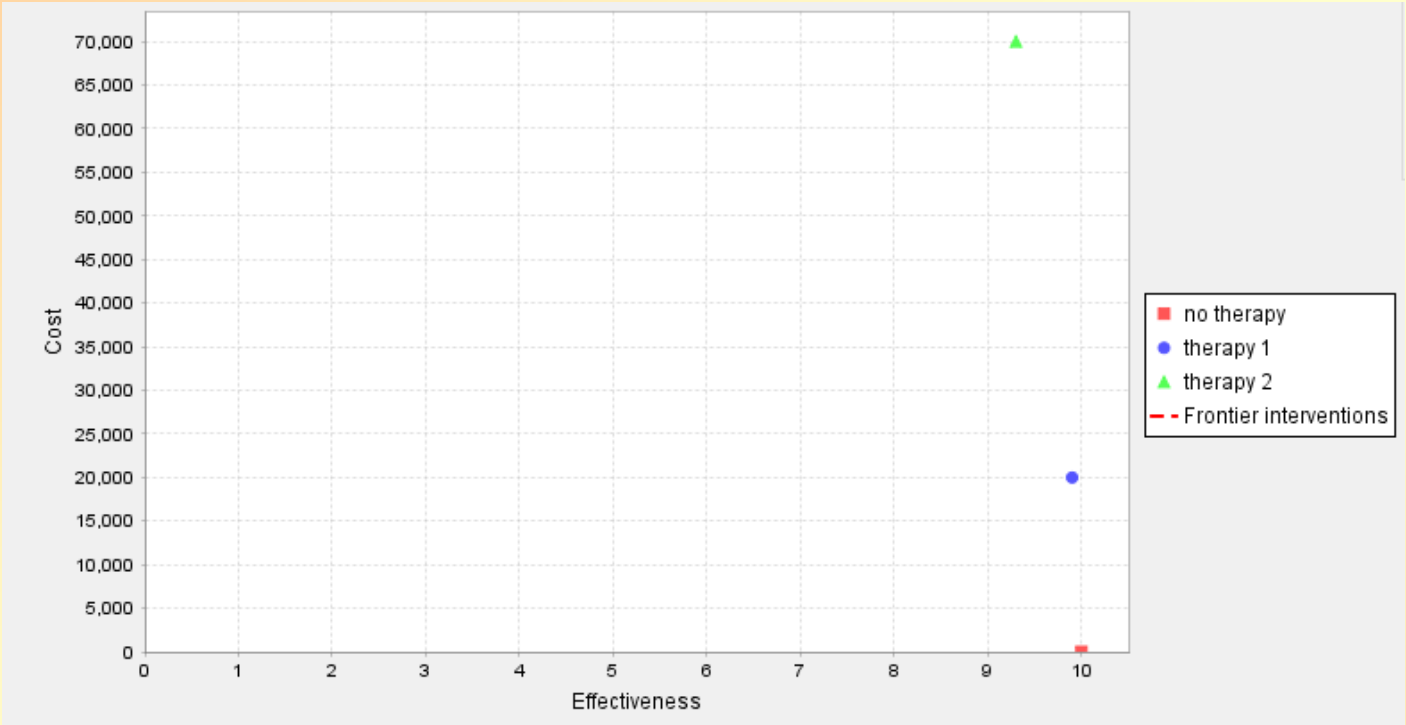
When we know that the disease is present



Interval for λ	Cost	Effect.	Best therapy
(0, 7,143)	0	1.2	no-therapy
(7,143, 13,208)	20.000	4.0	therapy-1
(13,208, +∞)	70.000	6.5	therapy-2



When we know that the disease is absent



Interval for λ	Cost	Effect.	Best therapy
(0, +∞)	0	10	no-therapy

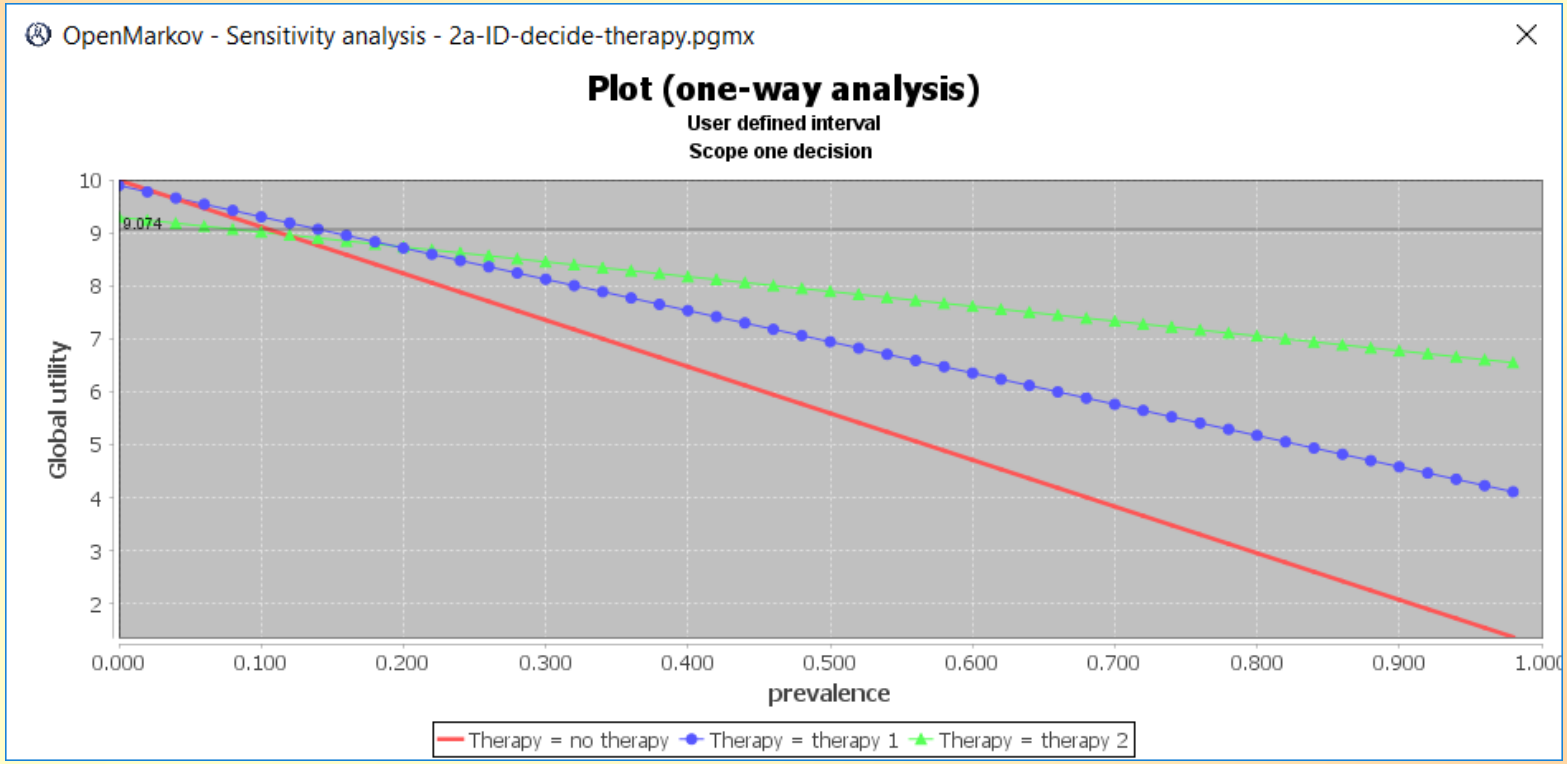
5.2. CEA with uncertainty about the disease

Cost-effectiveness of a test

- Prevalence of the disease: 0.14
- There is a test
  - sensitivity: 0.90
  - specificity 0.93
  - cost: € 150
- Questions:
  - Is the test cost-effective?
  - The answer depends on λ
  - What is the most beneficial therapy for each value of λ?
  - What is the ICER of the test?

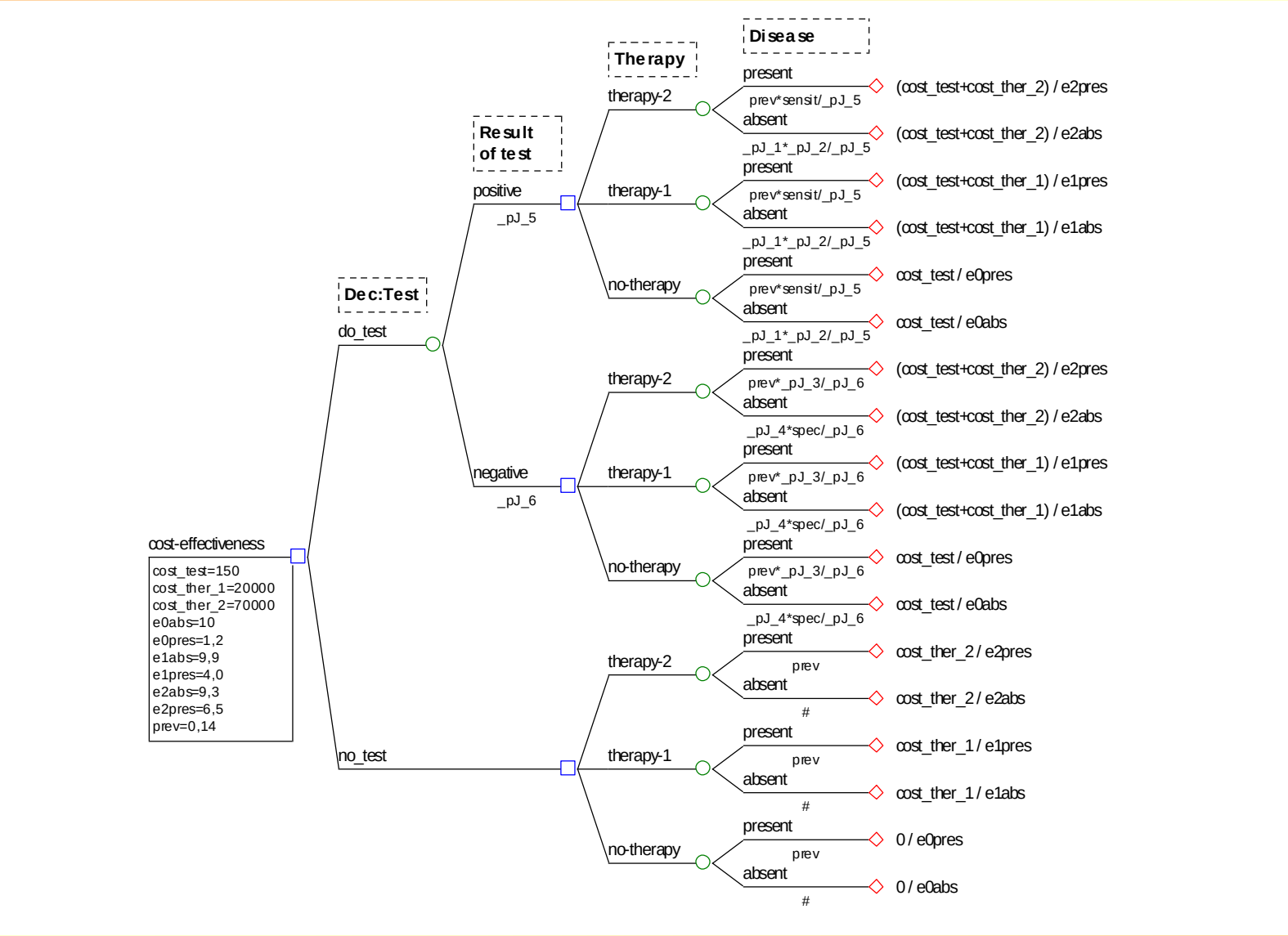
Effectiveness as a function of probability

- Before doing the test, it only depends on the prevalence:



- The result of the test changes the probability of the disease.

A decision tree for this example



Problem: the standard algorithm only works for the unicriterion case

A warning and a (rudimentary) solution

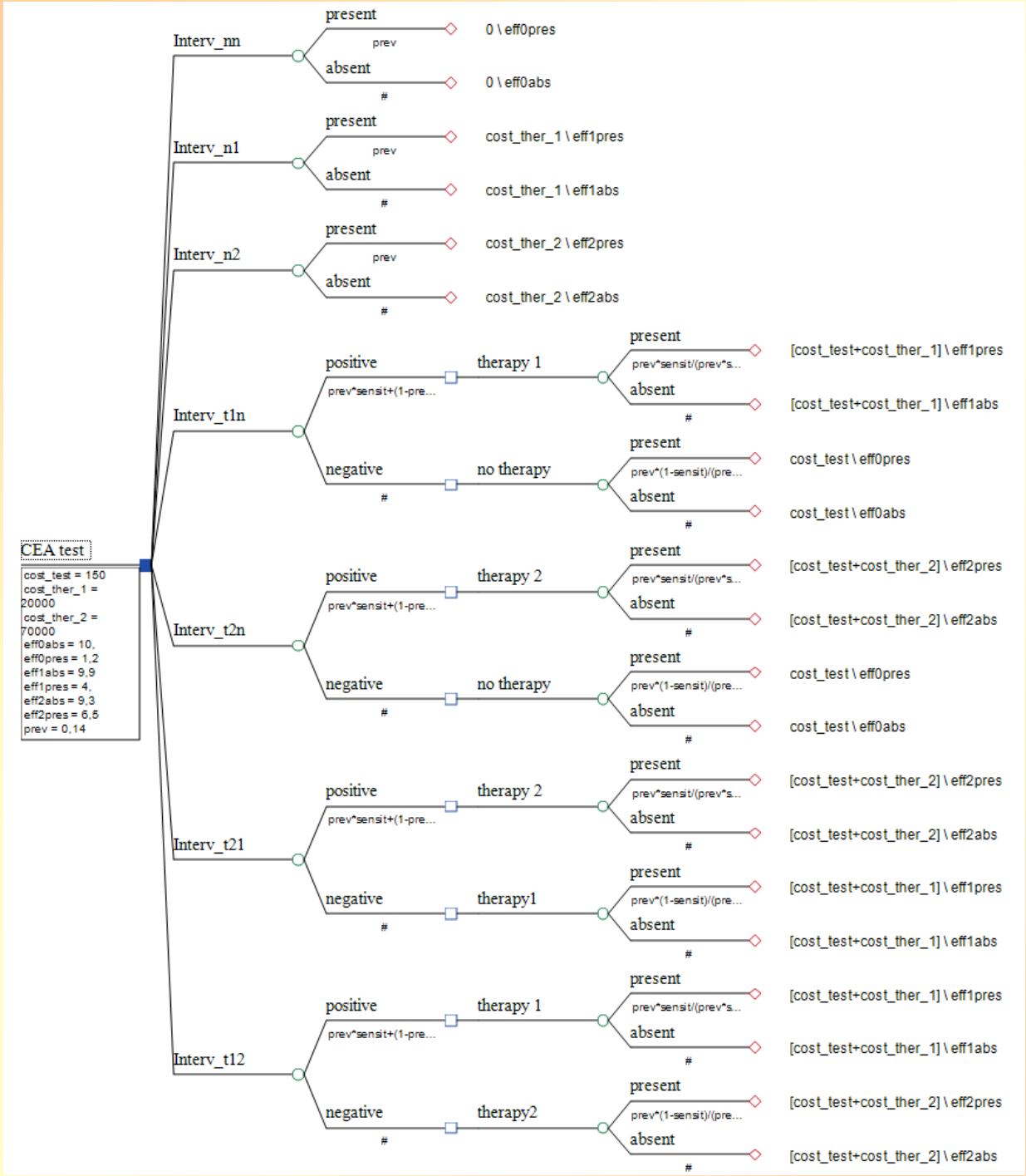
"Embedded, or downstream, decision nodes are not useful in cost-effectiveness analysis because the optimal branch cannot be determined when folding back the tree without an explicit decision rule for comparing costs and consequences.

Cost-effectiveness analyses can be performed with a decision tree that has one decision node at the root. The branches of the initial decision node represent all of the strategies that are to be compared."

[Kuntz and Weinstein, 2001]

How many strategies for this example?

- Without testing
  - No therapy in any case
  - Always therapy 1
  - Always therapy 2
- With testing
  - ~~If positive, no therapy; if negative, no therapy.~~
  - ~~If positive, no therapy; if negative, therapy 1.~~
  - ~~If positive, no therapy; if negative, therapy 2.~~
  - If positive, therapy 1; if negative, no therapy.
  - ~~If positive, therapy 1; if negative, therapy 1.~~
  - If positive, therapy 1; if negative, therapy 2.
  - If positive, therapy 2; if negative, no therapy.
  - If positive, therapy 2; if negative, therapy 1.
  - ~~If positive, therapy 2; if negative, therapy 2.~~


CEA test
cost_test = 150
cost_ther_1 = 20000
cost_ther_2 = 70000
eff0abs = 10,
eff0pres = 1,2
eff1abs = 9,9
eff1pres = 4,
eff2abs = 9,3
eff2pres = 6,5
prev = 0,14
Interv_nn
present
prev
0 \ eff0pres
absent
#
0 \ eff0abs
Interv_n1
present
prev
cost_ther_1 \ eff1pres
absent
#
cost_ther_1 \ eff1abs
Interv_n2
present
prev
cost_ther_2 \ eff2pres
absent
#
cost_ther_2 \ eff2abs
Interv_t1n
positive
prev*sensit+(1-pre...
therapy 1
present
prev*sensit/(prev*s...
[cost_test+cost_ther_1] \ eff1pres
absent
#
[cost_test+cost_ther_1] \ eff1abs
negative
#
no therapy
present
prev*(1-sensit)/(pre...
cost_test \ eff0pres
absent
#
cost_test \ eff0abs
Interv_t2n
positive
prev*sensit+(1-pre...
therapy 2
present
prev*sensit/(prev*s...
[cost_test+cost_ther_2] \ eff2pres
absent
#
[cost_test+cost_ther_2] \ eff2abs
negative
#
no therapy
present
prev*(1-sensit)/(pre...
cost_test \ eff0pres
absent
#
cost_test \ eff0abs
Interv_t21
positive
prev*sensit+(1-pre...
therapy 2
present
prev*sensit/(prev*s...
[cost_test+cost_ther_2] \ eff2pres
absent
#
[cost_test+cost_ther_2] \ eff2abs
negative
#
therapy1
present
prev*(1-sensit)/(pre...
[cost_test+cost_ther_1] \ eff1pres
absent
#
[cost_test+cost_ther_1] \ eff1abs
Interv_t12
positive
prev*sensit+(1-pre...
therapy 1
present
prev*sensit/(prev*s...
[cost_test+cost_ther_1] \ eff1pres
absent
#
[cost_test+cost_ther_1] \ eff1abs
negative
#
therapy2
present
prev*(1-sensit)/(pre...
[cost_test+cost_ther_2] \ eff2pres
absent
#
[cost_test+cost_ther_2] \ eff2abs

PharmacoEconomics (2014) 32:1141–1145
DOI 10.1007/s40273-014-0195-1

RESEARCH LETTER

The Problem of Embedded Decision Nodes in Cost-Effectiveness Decision Trees

Manuel Arias · Francisco Javier Díez

Published online: 31 July 2014

1 Introduction

Cost-effectiveness analysis (CEA) is increasingly used to inform health policies. Decision trees are the standard method for decision analysis in non-temporal domains. A decision node that is not the root of the tree is said to be embedded.

All books on medical decision analysis discuss both CEA *and* decision trees [1–11], but few explain how to conduct a CEA *with* decision trees [1, 2, 10, 11], and only build a decision tree with one decision node at the root, which represents all the strategies to be evaluated, as proposed by Kuntz and Weinstein; the other is to apply the algorithm presented in Arias and Díez [13].

As a case study, we consider the common problem of finding the incremental cost-effectiveness ratio (ICER) of a test:

Example 1 For a disease with a prevalence of 0.14, there are two possible therapies, the effectiveness of which depends on whether or not the disease is present, as shown

Technical Report

M. Arias and F. J. Díez. **Cost-effectiveness analysis with sequential decisions.** Technical Report CISIAD-11-01, UNED, Madrid, 2011.

26 pages. PDF (859 KB), zip version (827 KB), BibTeX entry.

Abstract

In this paper we present a new method for performing cost-efectiveness analysis of problems that involve multiple decisions and probabilistic outcomes. This problem has been ignored by most of the literature on medical decision making, and the few solutions proposed so far are either wrong or unfeasible except for very small problems. The method proposed in this paper consists of building a decision tree with several decision nodes and evaluating it with a modified roll-back algorithm that operates with partitions of intervals.

Decision trees

See the technical report for an explanation of these examples.

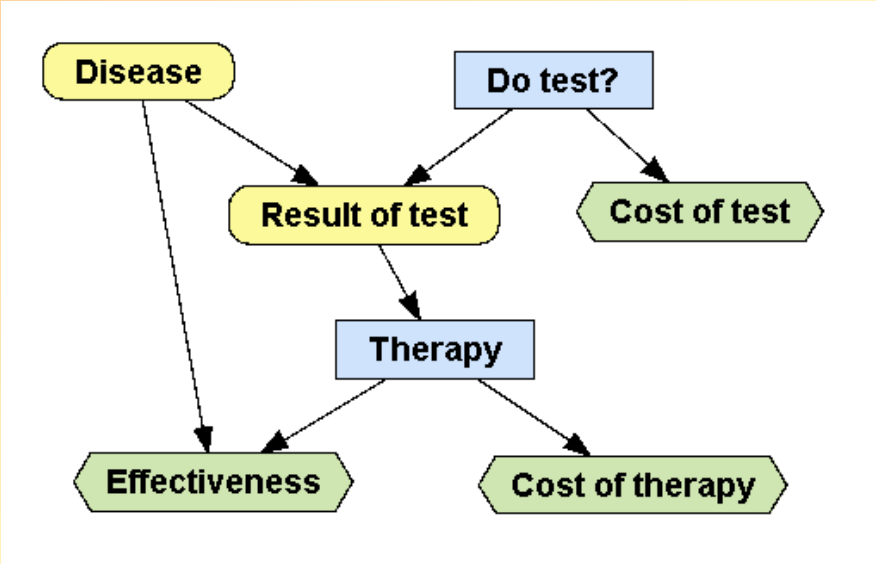
- natural tree (WinDM)
- natural tree (TreeAge Pro)
- all-strategies tree (TreeAge Pro)

Additional information

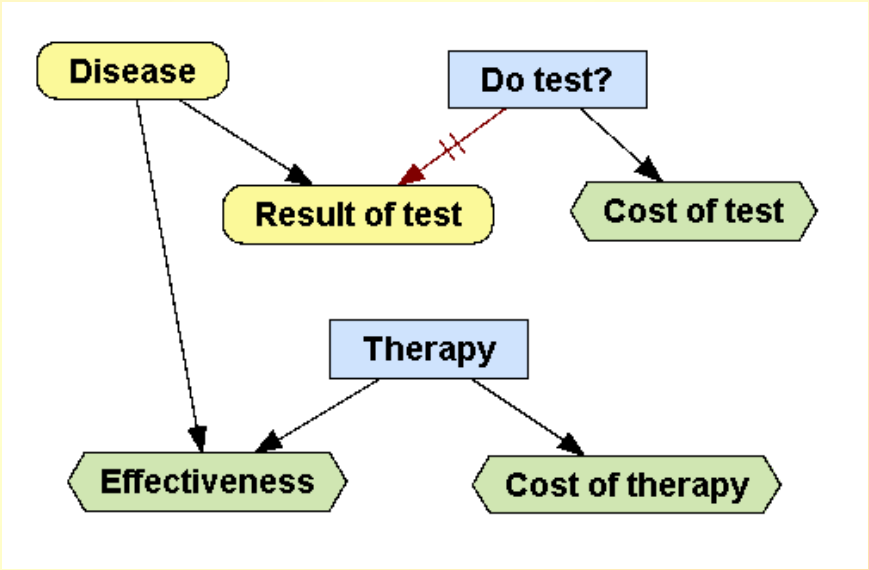
- Slides presented at SMDM-2007.
- Cost-effectiveness analysis in OpenMarkov.

5.3. CEA with IDs and DANs

Influence diagram



DAN



- The same structure as in the unicriterion case
- but now we have <u>two criteria</u>: cost and effectiveness

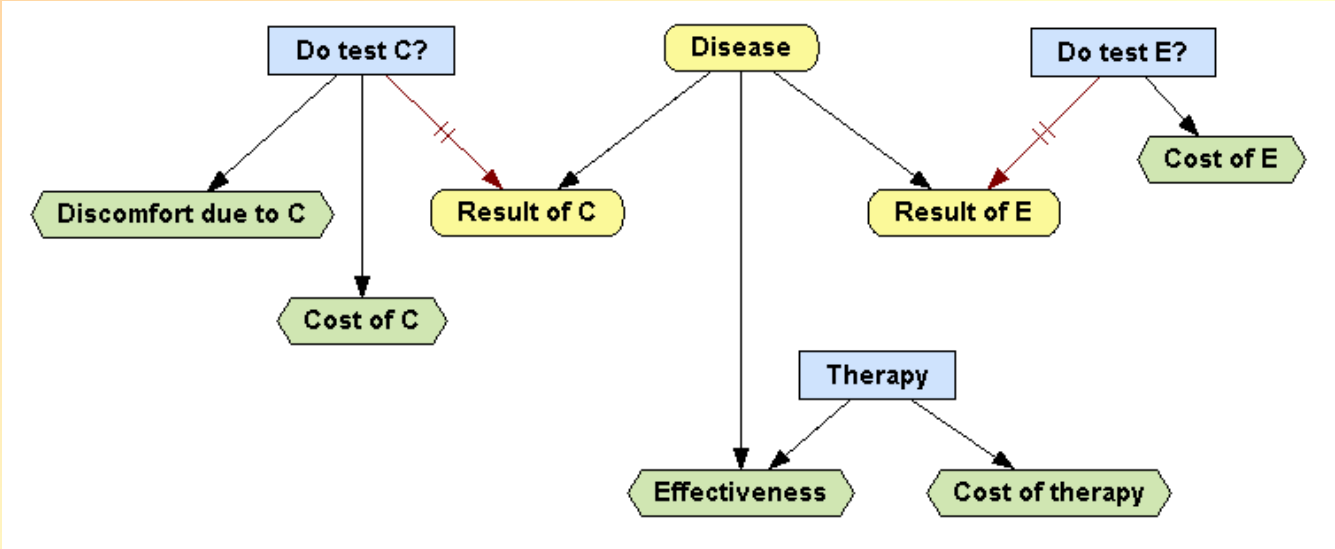
An example with two tests

- The same disease and therapies as in the previous example.
- Test E (the same as in the previous example)
  - sensitivity: 0.90
  - specificity: 0.93
  - cost: €150
- Test C
  - sensitivity: 0.78
  - specificity: 0.91
  - cost: €18
  - discomfort: 0.001 QALY
- What is the optimal policy (for each value of λ)?

It is a difficult problem

- Impossible to solve this problem with an ID
  - IDs require a total ordering of the decisions
  - The trick of using two IDs does not work in this case because it does not return all the ICERs
- Difficult to build a decision tree with embedded dec. nodes
  - It would have 90 leaves
  - Computing the probability of each scenario is cumbersome
- Much more difficult to build a decision tree without embedded decision nodes
  - Finding the possible interventions is a daunting task

… that can be easily solved with a DAN



λ_{inf} (€/QALY)	λ_{sup} (€/QALY)	cost (€)	effect. (QALY)	policy
0	7,747	0	8.768	do nothing
7,747	21,385	2,120	9.046	do test C; if positive {do test E; if positive, therapy 1}
21,385	24,090	7,305	9.284	do test C; if positive {do test E; if positive, therapy 2}
24,090	74,131	9,062	9.357	do test E; if positive {do test C; if negative, therapy 1; if positive, therapy 2}
74,131	112,564	10,735	9.380	do both tests; if both are positive, therapy 2; if only one is positive, therapy 1
112,564	$+\infty$	14,857	9.416	do test E; if positive, therapy 2; if negative {do test C; if positive, therapy 1}

Methods of Information in Medicine 2015;54:353-358.

Cost-effectiveness Analysis with Influence Diagrams*

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Keywords

Cost-benefit analysis, cost-effectiveness analysis, decision trees, influence diagrams

Summary

Background: Cost-effectiveness analysis (CEA) is used increasingly in medicine to determine whether the health benefit of an intervention is worth the economic cost. Decision trees, the standard decision modeling technique for non-temporal domains, can only perform CEA for very small problems.

Objective: To develop a method for CEA in problems involving several dozen variables.

Methods: We explain how to build influence diagrams (IDs) that explicitly represent cost and effectiveness. We propose an algorithm for evaluating cost-effectiveness IDs directly, i.e., without expanding an equivalent deci-

Results: The evaluation of an ID returns a set of intervals for the willingness to pay – separated by cost-effectiveness thresholds – and, for each interval, the cost, the effectiveness, and the optimal intervention. The algorithm that evaluates the ID directly is in general much more efficient than the brute-force method, which is in turn more efficient than the expansion of an equivalent decision tree. Using OpenMarkov, an open-source software tool that implements this algorithm, we have been able to perform CEAs on several IDs whose equivalent decision trees contain millions of branches.

Conclusion: IDs can perform CEA on large problems that cannot be analyzed with decision trees.

units divided by cost units; for example, in dollars per death avoided or euros per quality-adjusted life year (QALY) [4]. As the willingness to pay is different for each decision maker, CEA must consider all its possible values. The result of the analysis is usually a set of intervals for λ, each one having an optimal intervention.

When the consequences of the interventions are not deterministic, it is necessary to model the probability of each outcome. Decision trees are the tool used most frequently for this task, especially in medicine [5]. Their main drawback is that their size grows exponentially with the number of variables[b]. In the medical literature, trees usually have 3 or 4 variables and between 6 and 10 leaf nodes. A tree of 5 variables typically contains around 20 leaf nodes,

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Position Paper

Cost-effectiveness analysis with unordered decisions

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ARTICLE INFO

Keywords:
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Decision trees
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Influence diagrams
Decision analysis networks

ABSTRACT

Introduction: Cost-effectiveness analysis (CEA) is used increasingly in medicine to determine whether the health benefit of an intervention is worth the economic cost. Decision trees, the standard decision modeling technique for non-temporal domains, can only perform CEAs for very small problems. Influence diagrams can model much larger problems, but only when the decisions are totally ordered.
Objective: To develop a CEA method for problems with unordered or partially ordered decisions, such as finding the optimal sequence of tests for diagnosing a disease.
Methods: We explain how to model those problems using decision analysis networks (DANs), a new type of probabilistic graphical model, somewhat similar to Bayesian networks and influence diagrams. We present an algorithm for evaluating DANs with two criteria, cost and effectiveness, and perform some experiments to study its computational efficiency. We illustrate the representation framework and the algorithm using a hypothetical example involving two therapies and several tests and then present a DAN for a real-world problem, the mediastinal staging of non-small cell lung cancer.
Results: The evaluation of a DAN with two criteria, cost and effectiveness, returns a set of intervals for the willingness to pay, separated by incremental cost-effectiveness ratios (ICERs). The cost, the effectiveness, and the optimal intervention are specific for each interval, i.e., they depend on the willingness to pay.
Conclusion: Problems involving several unordered decisions can be modeled with DANs and evaluated in a reasonable amount of time. OpenMarkov, an open-source software tool developed by our research group, can be used to build the models and evaluate them using a graphical user interface.

Hands-on exercise 4

Exercise: cost-effectiveness for two tests

Test	sensitivity	specificity	discomfort	cost
A	0.60	0.92	0.0003 QALY	$100
B	0.80	0.91	0.0001 QALY	$200

Disease →	absent	present
therapy	38 QALY	30 QALY
no therapy	40 QALY	20 QALY

cost of therapy = $7,000

- The same probabilities and effectiveness as in exercise 3
- but now we are also considering economic costs.
- Question: What is the most beneficial strategy?

6. Temporal models

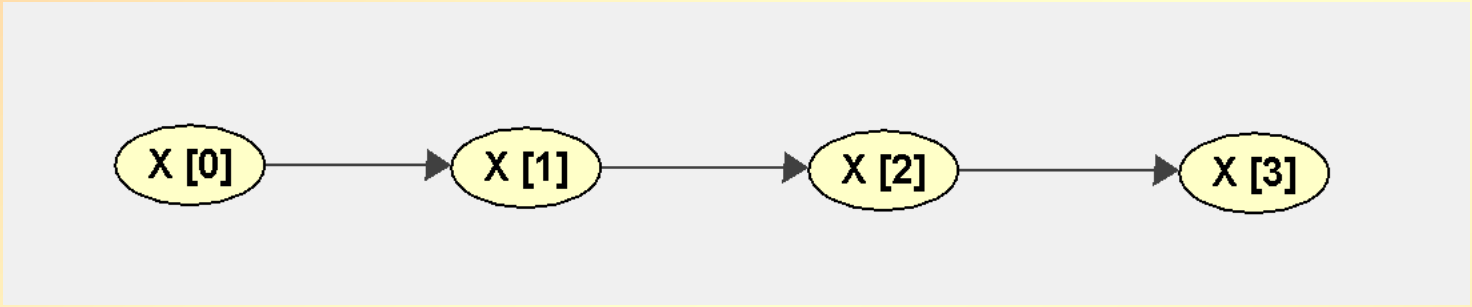
Temporal PGMs

- Markov models
  - The future is independent of the past given the present
    - "Markov models do not have memory"
  - Key concept: state
  - Types of models: Markov chains, HMMs, MDPs, POMDPs, DBNs, MIDs, DLIMIDs…

- Temporal non-Markovian models
  - The future is **not** determined by the current state
    - for example, birth occurs around 9 months after conception
  - An type of non-Markov model: event networks
    - Galán, Aguado, Díez, Mira. NasoNet: Modelling the spread of nasopharyngeal cancer with temporal Bayesian networks. *AI in Med*, 2002.

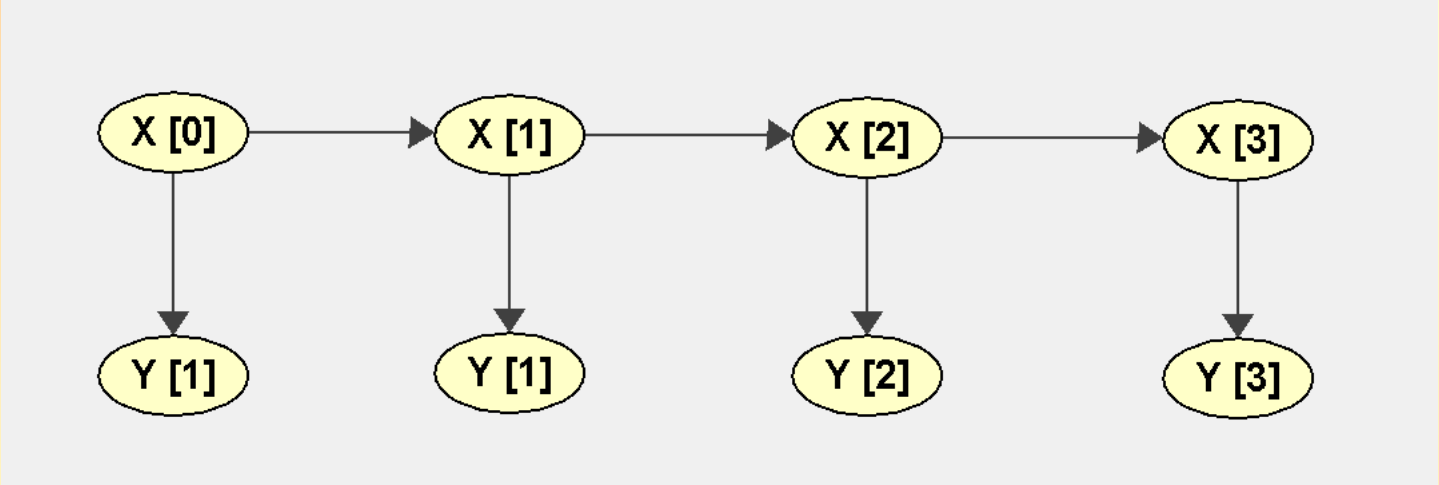
6.1. Types of Markov models

Markov chain



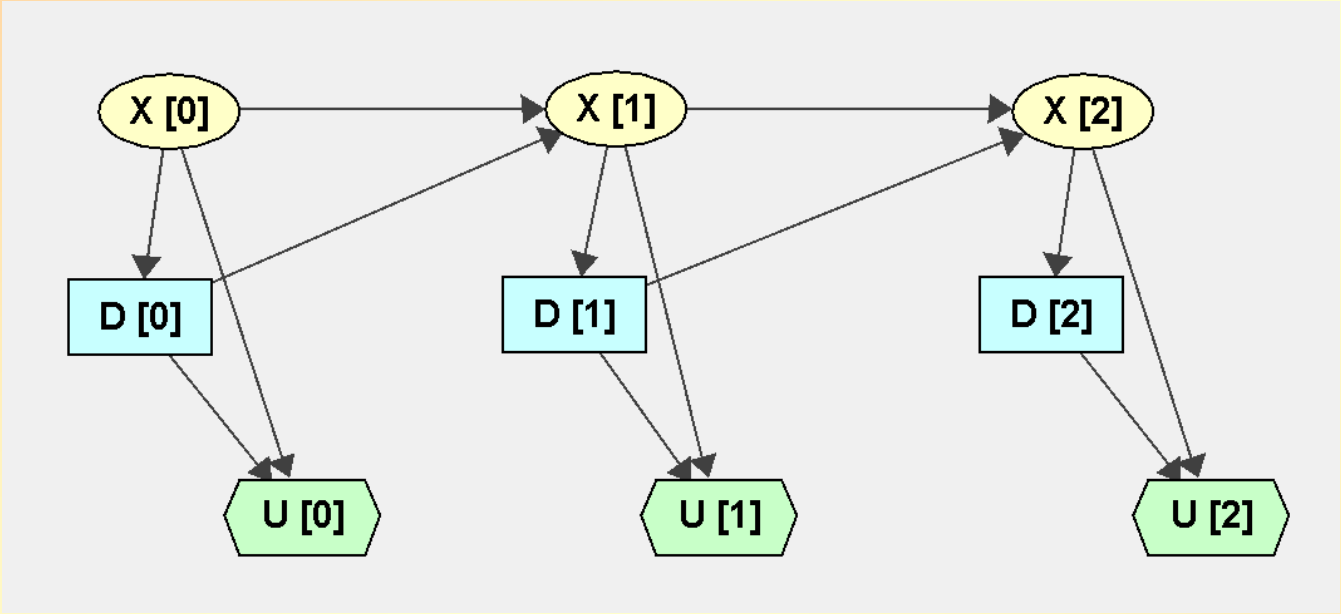
- One variable that evolves over time
- Transition probabilities: $P(x_{i+1}|x_i)$

Hidden Markov model (HMM)



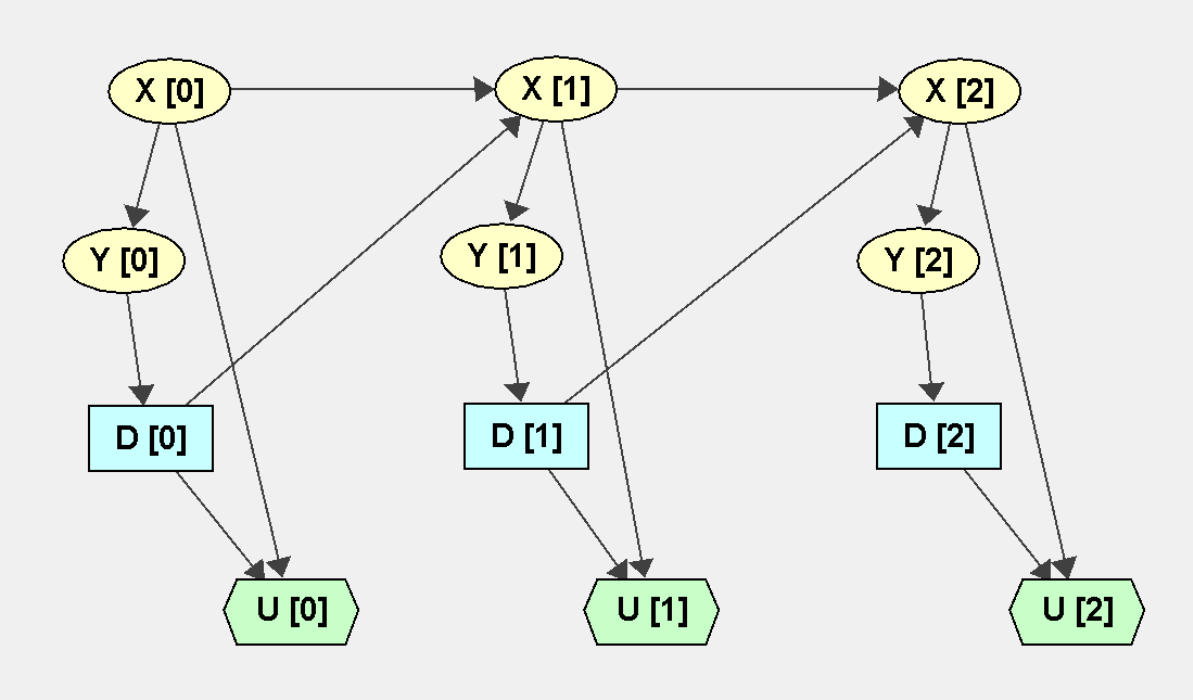
- Observed variable: Y
- Non-observed (hidden) variable: X
- Transition probabilities: $P(x_{i+1}|x_i)$
- Probability of each observation: $P(y_i|x_i)$

Markov decision process (MDP)



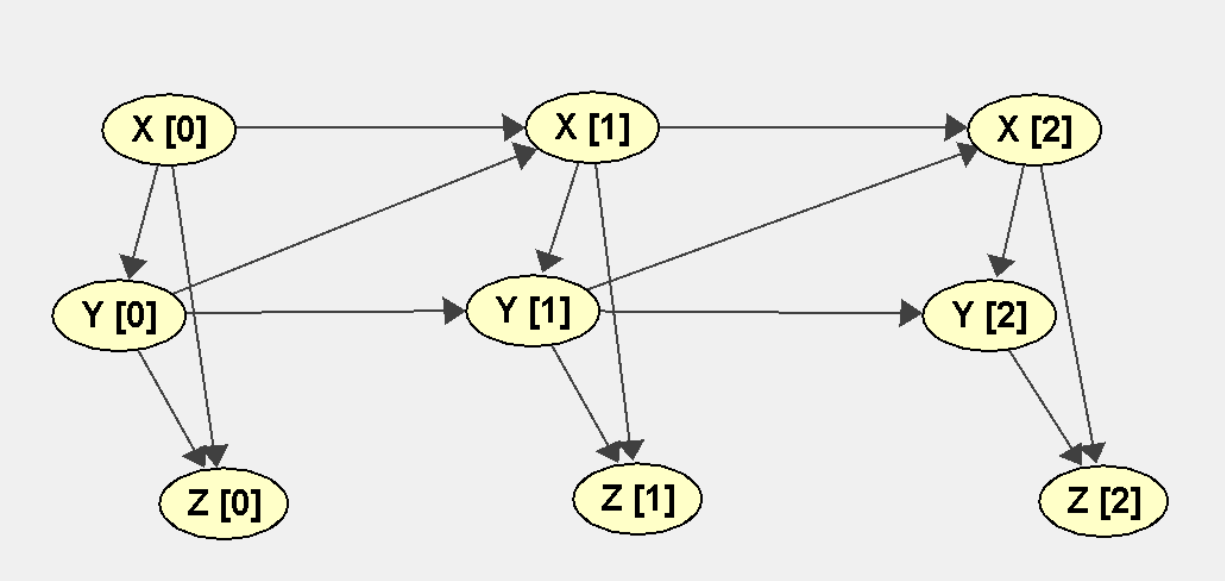
- Observed variable: X
- Decision: D
- Transition probabilities: $P(x_{i+1}|x_i, d_i)$
- Reward: $U(x_i, d_i)$

Partially observable MDP (POMDP)



- Hidden variable: X
- Observed variable : Y
- Decision: D
- Observation prob.: $P(y_i|x_i)$
- Transition prob.: $P(x_{i+1}|x_i, d_i)$
- Reward: $U(x_i, d_i)$

Dynamic Bayesian network (DBN)



- Markov chain or hidden Markov model:
  - one variable, X
  - one conditional probability: $P(x_{i+1}|x_i)$
- Dynamic Bayesian network:
  - several variables, $\{X, Y, Z\ldots\}$
  - factored probability: $P(y_i|x_i)$, $P(z_i|x_i, y_i)$, $P(x_{i+1}|x_i, y_i)\ldots$

Factored extensions of Markov models

Flat model	Factored model
Markov chain	Dynamic Bayesian network [Dean and Kanazawa, 1989]
Hidden Markov model	
Markov decision process (MDP)	Factored MDP [Boutilier et al., 1995, 2000]
Partially-observable MDP (POMDP)	Factored POMDP [Boutilier and Poole, 1996]

IJCAI Workshop *Decision Making in Partially Observable, Uncertain Worlds: Exploring Insights from Multiple Communities*
Barcelona, Spain, July 2011

MDPs in Medicine: Opportunities and Challenges

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Abstract

In the last three decades hundreds of Markov models have been built for medical applications, but most of them fall under the paradigm of what we call *simple Markov models* (SMMs). Markov decision processes (MDPs) are much more powerful as a decision analysis tool, but they are ignored in medical decision analysis books and the number of medical applications based on them is still very small. In this paper we compare both types of models and discuss the challenges that MDPs must overcome before they can be widely accepted in medicine. We present a software tool, OpenMarkov, that addresses those challenges and has been used to build a Markov model for analyzing the cost-effectiveness of the HPV vaccine.

1 Introduction

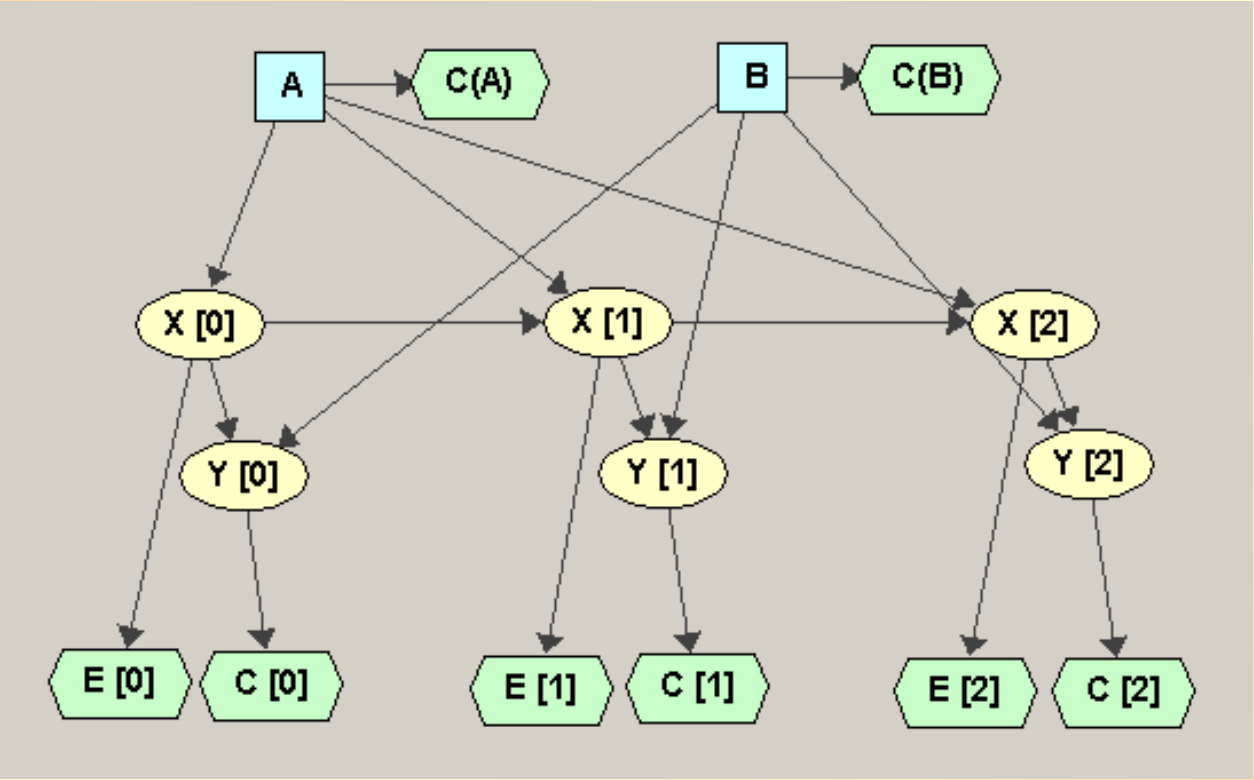
Markov models were introduced in the beginning of the 20-th century by the Russian mathematician Andrei Andreyevich Markov [1906]. In the three decades passed since the pioneering work of Beck and Pauker [1983], hundreds of

the emergence of partially observable Markov decision processes (POMDPs) [Åström, 1965], in which the state of the system is not directly observable, but there is a variable that correlates probabilistically with it. POMDPs were developed in the field of automatic control as an extension of MDPs, but currently most of the research about them is carried out in artificial intelligence (AI), again as a tool for planning, especially in robotics [Ghallab *et al.*, 2004]. The main contribution of AI to this field comes from the area of probabilistic graphical models: Bayesian networks [Pearl, 1988] led to the development of dynamic Bayesian networks [Dean and Kanazawa, 1989], which generalize Markov chains and hidden Markov models [Murphy, 2002]. The idea of using several variables to represent the state of the system, instead of only one, led to factored MDPs [Boutilier *et al.*, 1995; 2000] and factored POMDPs [Boutilier and Poole, 1996], which can model efficiently many problems that were unmanageable with flat (i.e., non-factored) representations; correspondingly, there are new algorithms that can solve problems several orders of magnitude bigger than in the recent past [Hoey *et al.*, 1999; Poupart, 2005; Spaan and Vlassis, 2005].

In the rest of the paper, we use the acronym MDPs to refer to both fully observable and partially observable models (FOMDPs and POMDPs, respectively).

6.2. Markov influence diagrams

Markov influence diagrams



- Tractable only when decisions are atemporal, i.e., policies do not change over time
- Can be used for cost-effectiveness analysis

Medical Decision Making 2017; 37:183-195

ORIGINAL ARTICLE

Markov Influence Diagrams: A Graphical Tool for Cost-Effectiveness Analysis

Francisco J. Díez, PhD, Mar Yebra, MEng, Iñigo Bermejo, PhD, Miguel A. Palacios-Alonso, MSc, Manuel Arias Calleja, PhD, Manuel Luque, PhD, Jorge Pérez-Martín, MEng

Markov influence diagrams (MIDs) are a new type of probabilistic graphical model that extends influence diagrams in the same way that Markov decision trees extend decision trees. They have been designed to build state-transition models, mainly in medicine, and perform cost-effectiveness analyses. Using a causal graph that may contain several variables per cycle, MIDs can model various patient characteristics without multiplying the number of states; in particular, they can represent the history of the patient without using tunnel states. OpenMarkov, an open-source tool, allows the decision analyst to build and evaluate MIDs—including cost-effectiveness analysis and several types of deterministic and probabilistic sensitivity analysis—with a graphical user interface, without writing any code. This way, MIDs can be used to easily build and evaluate complex models whose implementation as spreadsheets or decision trees would be cumbersome or unfeasible in practice. Furthermore, many problems that previously required discrete event simulation can be solved with MIDs; i.e., within the paradigm of state-transition models, in which many health economists feel more comfortable. ***Key words:*** *Markov models; influence diagrams; cost-effectiveness analysis; outcomes research.* ***(Med Decis Making XXXX; XX:xx–xx)***

Hands-on exercise 5

A small Markov model

- A disease can be *latent* (QoL = 0.9) or *active* (QoL = 0.7).
- Two therapies
  - standard: $150/month when *latent*
$2,500/month when *active*
  - new therapy, only effective when *latent*: $950/month
- Monthly transition probabilities
  - *active* → *dead*: 15%
  - *latent* → *dead*: 2%
  - *latent* → *active*, standard therapy: 11%
  - *latent* → *active*, new therapy: 8%

  } effect of the new therapy

  - *active* → *latent* 0% (no regression)
- Annual discount rate: 3.5% for cost and effectiveness
- Is the new therapy cost-effective?

6.2.1. Example: Chancellor's model for HIV

Case study: HIV/AIDS
(Chancellor et al.,1997)

ORIGINAL RESEARCH ARTICLE

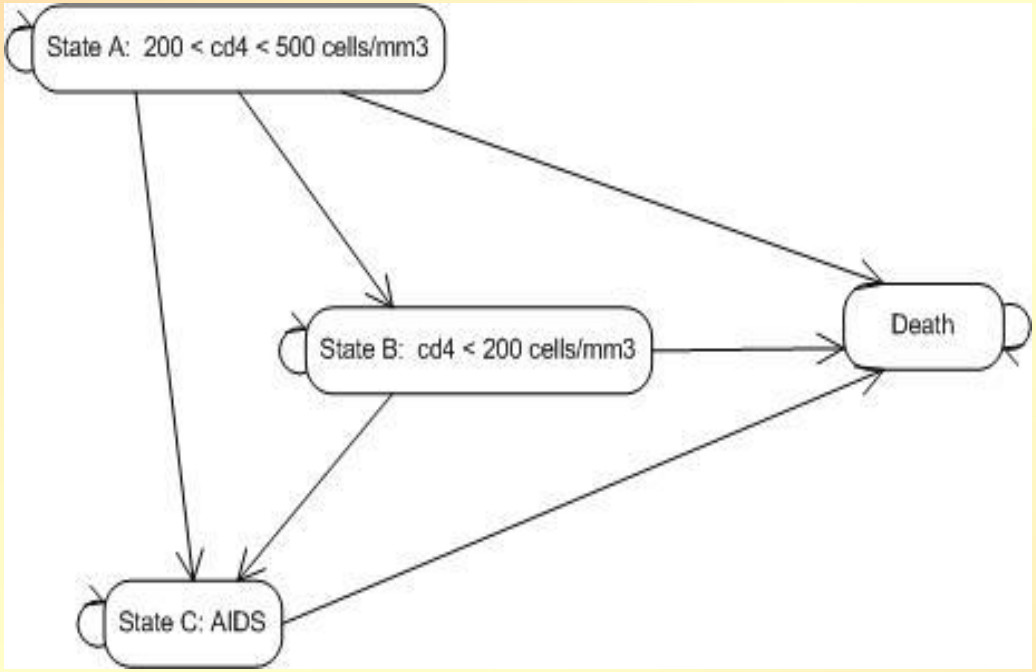
Pharmacoeconomics 1997 Jul 12 (1) 54-66
1170-7690/97/0007-0054/$06.50/0

Modelling the Cost Effectiveness of Lamivudine/Zidovudine Combination Therapy in HIV Infection

Jeremy V. Chancellor,[1] *Andrew M. Hill,*[2] *Caroline A. Sabin,*[3] *Kit N. Simpson*[4] and *Mike Youle*[5]

1 Glaxo Wellcome UK Ltd, Uxbridge, Middlesex, England
2 Glaxo Wellcome Research and Development Ltd, Greenford, Middlesex, England
3 Department of Primary Care and Population Sciences, Royal Free Hospital, London, England
4 University of North Carolina, Chapel Hill, North Carolina, USA
5 HIV/GUM Research Unit, Chelsea and Westminster Hospital, London, England

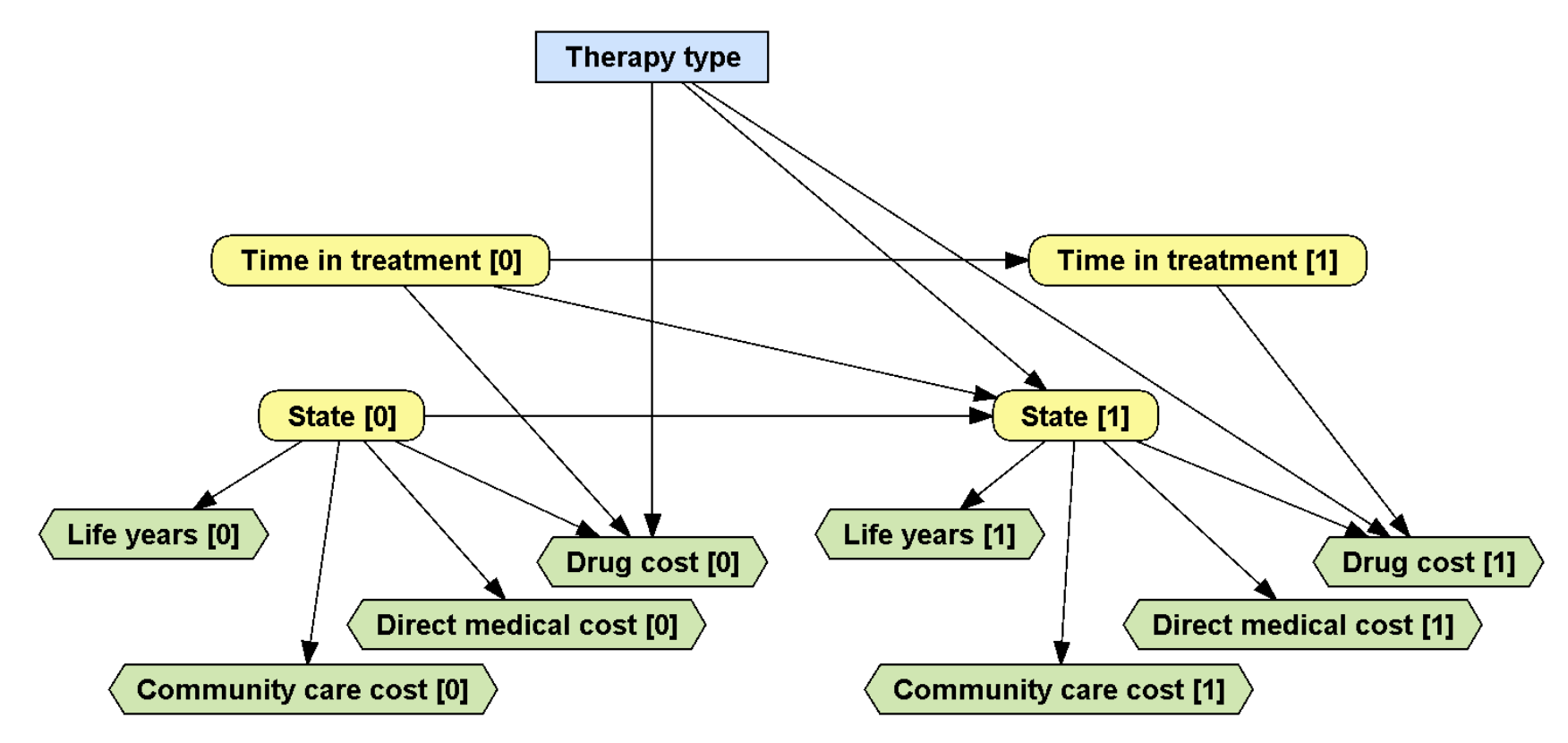
- State-transition diagram: 4 states



- Two therapies:
  - monotherapy: AZT only
  - combined therapy: AZT + lamivudine for 2 years; then only AZT

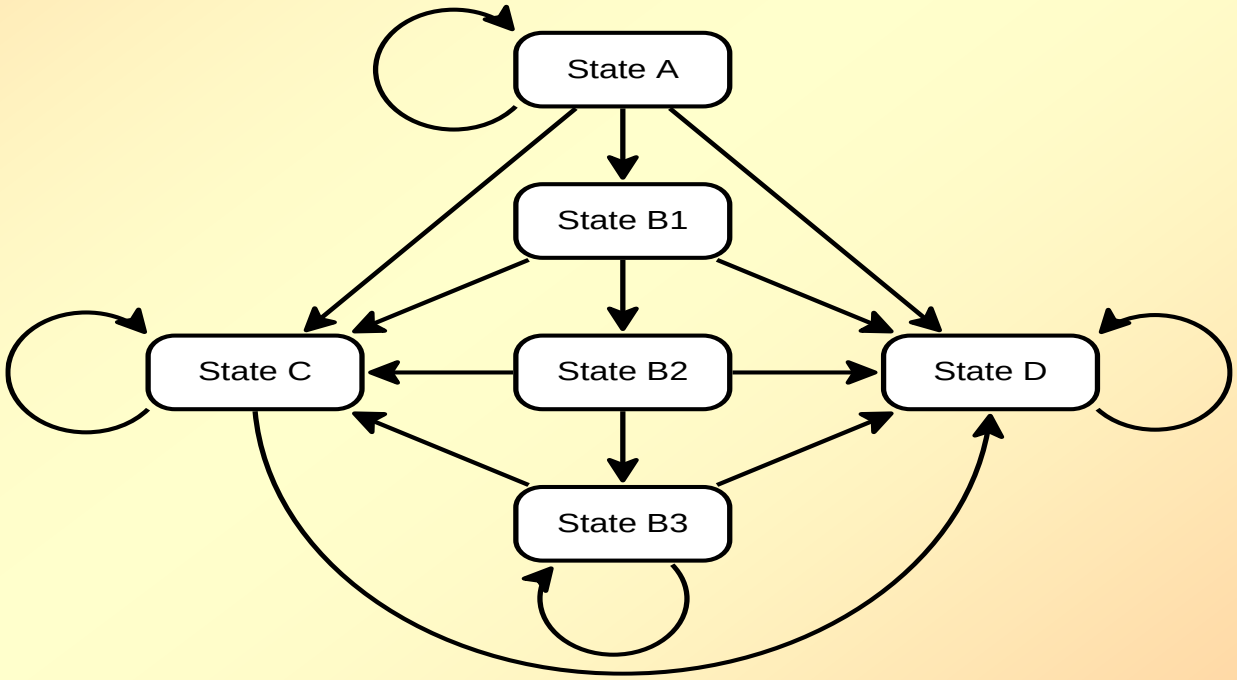
A MID version of the HIV model

[Chancellor et al., 1997]



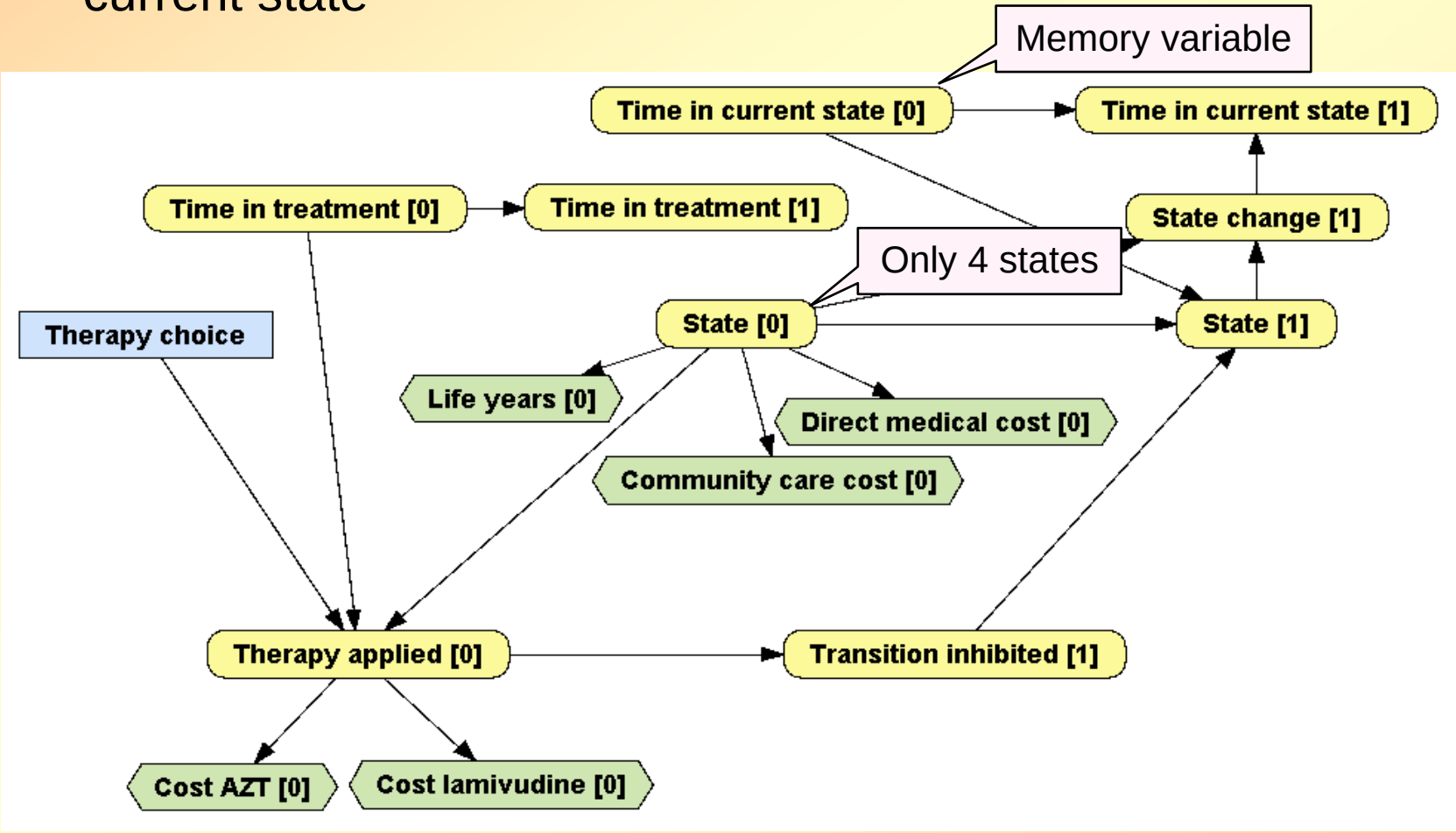
Representing the patient history (1)

- Transition probabilities that depend on the time spent in current state
  - We can build a state-transition model with tunnel states



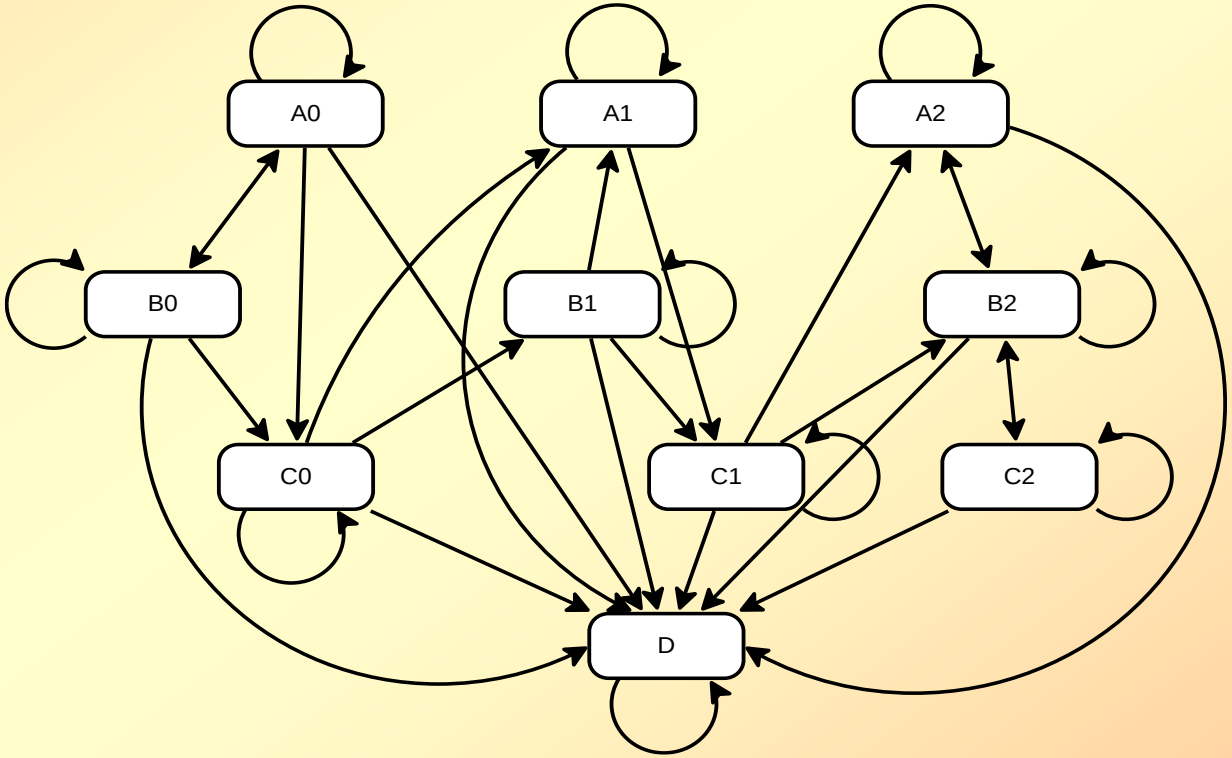
Representing the patient history (1)

- Transition probabilities that depend on the time spent in current state



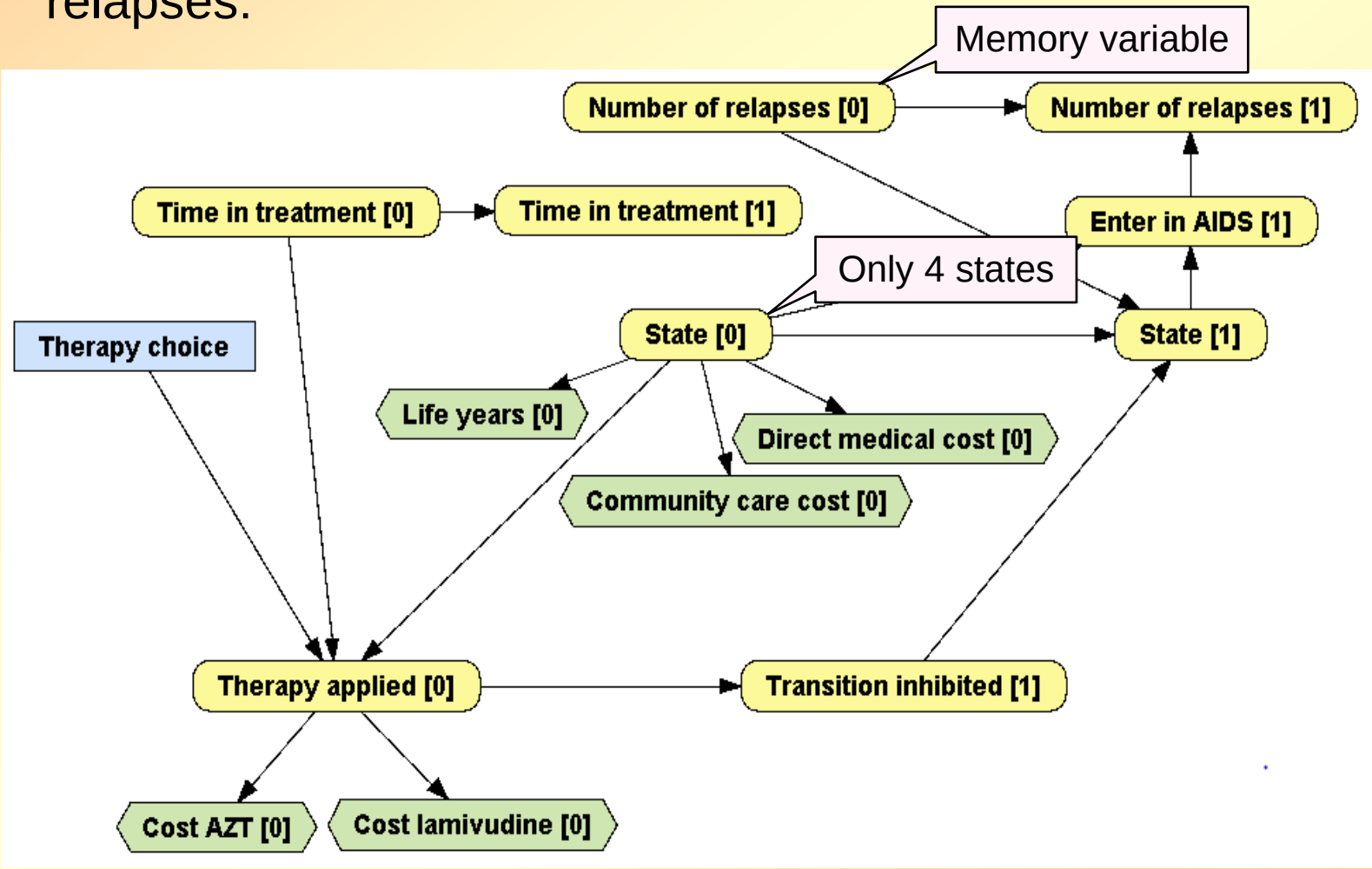
Representing the patient history (2)

- Transition probabilities that depend on the number of relapses
  - We can add states to keep track of the number of relapses



Representing the patient history (2)

- Transition probabilities that depend on the number of relapses:



6.2.2. Other MIDs for real-world problems

Case study: Hip replacement
(Briggs et al., 2004)

ARTICLE

Appl Health Econ Health Policy 2004; 3 (2): 79-89
1175-5652/04/0002-0079/$31.00/0

The Use of Probabilistic Decision Models in Technology Assessment

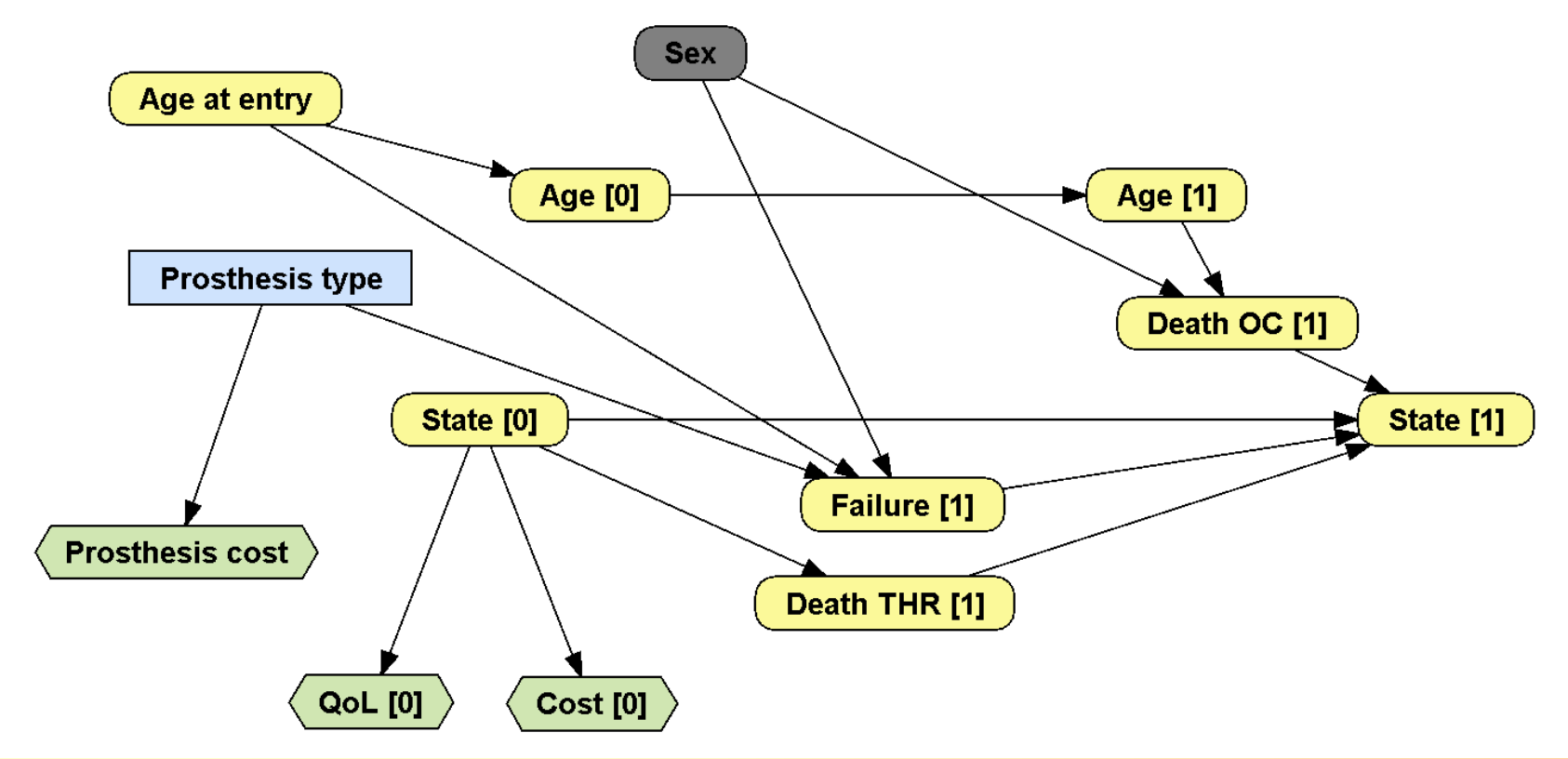
The Case of Total Hip Replacement

Andrew Briggs,[1] *Mark Sculpher*,[2] *Jill Dawson*,[3] *Ray Fitzpatrick*,[4] *David Murray*[5] and *Henrik Malchau*[6]

1 Health Economics Research Centre, Department of Public Health, University of Oxford, Old Road Campus, Headington, Oxford, UK
2 Centre for Health Economics, University of York, Heslington, York, UK
3 School of Health and Social Care, Oxford Brookes University, Oxford, UK
4 Department of Public Health, University of Oxford, Old Road Campus, Headington, Oxford, UK
5 Nuffield Orthopaedic Centre, Headington, Oxford, UK
6 Department of Orthopaedics, Massachusetts General Hospital, Boston, USA

A MID version of the hip replacement model

[Briggs et al., 2004]



Case study: HPV vaccine
(Insinga et al., 2009)

BMC Infectious Diseases

BioMed Central

Research article

Open Access

Epidemiologic natural history and clinical management of Human Papillomavirus (HPV) Disease: *a critical and systematic review of the literature in the development of an HPV dynamic transmission model*

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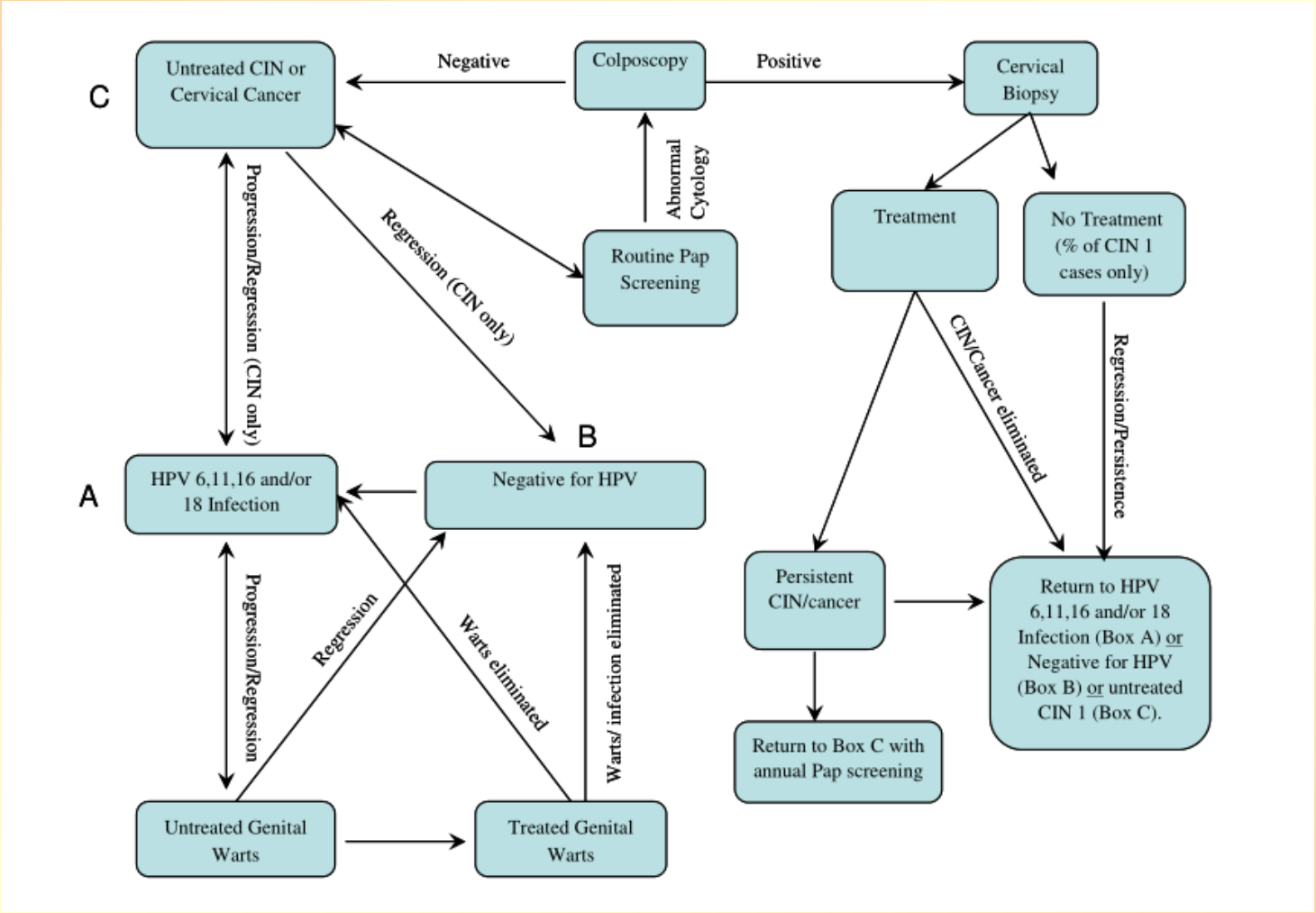
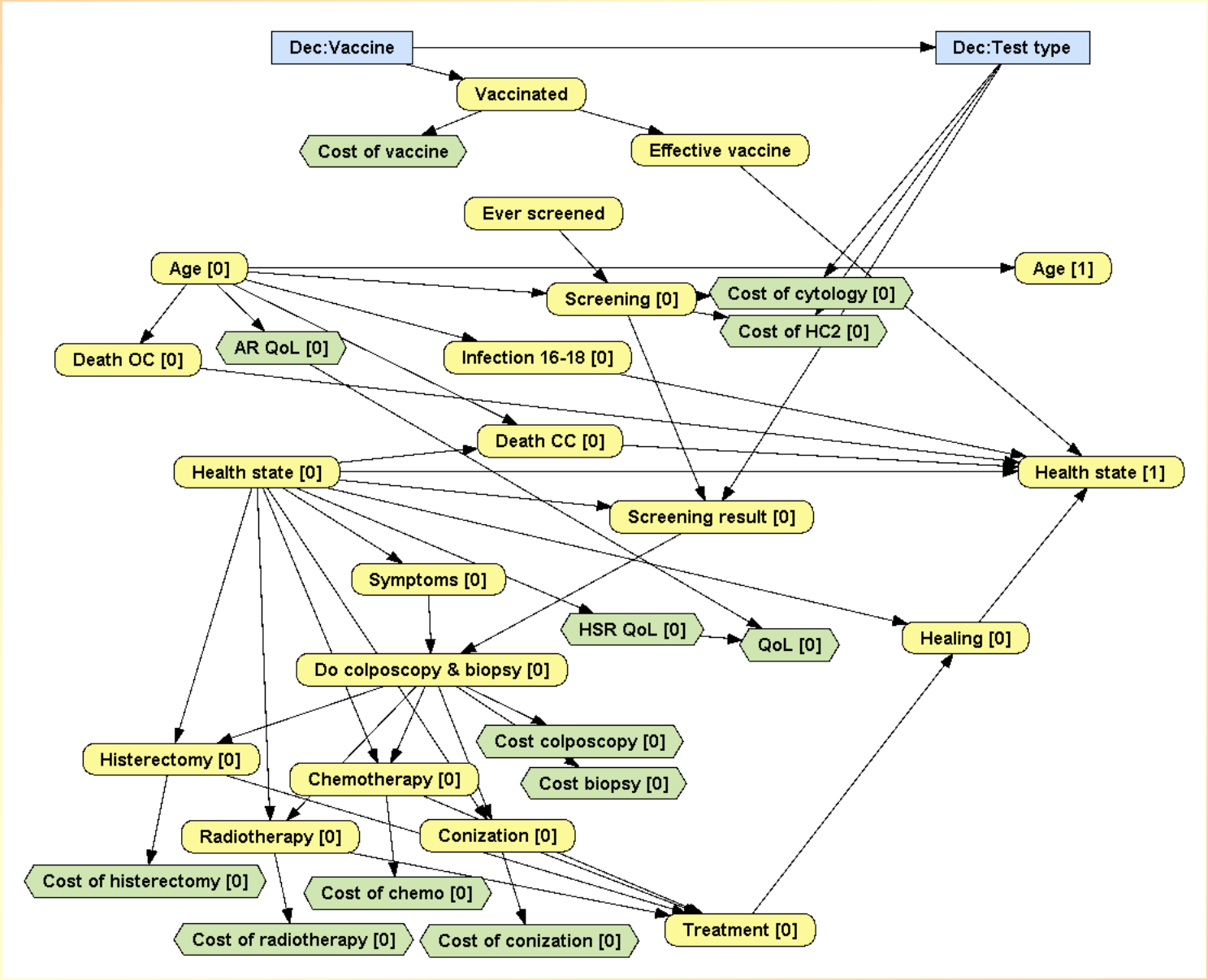

C
Untreated CIN or Cervical Cancer
Negative
Colposcopy
Positive
Cervical Biopsy
Abnormal Cytology
Routine Pap Screening
Progression/Regression (CIN only)
Regression (CIN only)
Treatment
No Treatment (% of CIN 1 cases only)
CIN/Cancer eliminated
Regression/Persistence
B
A
HPV 6,11,16 and/or 18 Infection
Negative for HPV
Progression/Regression
Regression
Warts eliminated
Warts/ infection eliminated
Persistent CIN/cancer
Return to HPV 6,11,16 and/or 18 Infection (Box A) or Negative for HPV (Box B) or untreated CIN 1 (Box C).
Return to Box C with annual Pap screening
Untreated Genital Warts
Treated Genital Warts

A MID version of the HPV vaccination model

[Callejo et al., 2010]



Content of one of the Excel cells for this model:

=VLOOKUP($C5;Variables!$A$4:$H$21;8;TRUE)*(((BI5+BJ5)+BK5*uCIN1+SUM(BL5:BP5)*uCIN2_3+(BQ5+BR5)*uLCC+(BS5+BT5)*uRCC+(BU5+BV5)*uDCC)+((BI4+BJ4)+BK4*uCIN1+SUM(BL4:BP4)*uCIN2_3+(BQ4+BR4)*uLCC+(BS4+BT4)*uRCC+(BU4+BV4)*uDCC)*VLOOKUP($C4;Variables!$A$4:$H$21;2;TRUE)+(BQ4+BR4)*uLCC*VLOOKUP($C4;Variables!$A$4:$H$21;4;TRUE)+(BS4+BT4)*uRCC*VLOOKUP($C4;Variables!$A$4:$H$21;5;TRUE)+(BU4+BV4)*uDCC*VLOOKUP($C4;Variables!$A$4:$H$21;2;TRUE))

Case study: AIDS in Africa
(Ryan et al., 2009)

The cost-effectiveness of cotrimoxazole prophylaxis in HIV-infected children in Zambia

Máirín Ryan[a], Susan Griffin[b], Bona Chitah[c], A. Sarah Walker[d], Veronica Mulenga[e], Donald Kalolo[e], Neil Hawkins[b], Concepta Merry[a], Michael G. Barry[a], Chifumbe Chintu[e], Mark J. Sculpher[b] and Diana M. Gibb[d]

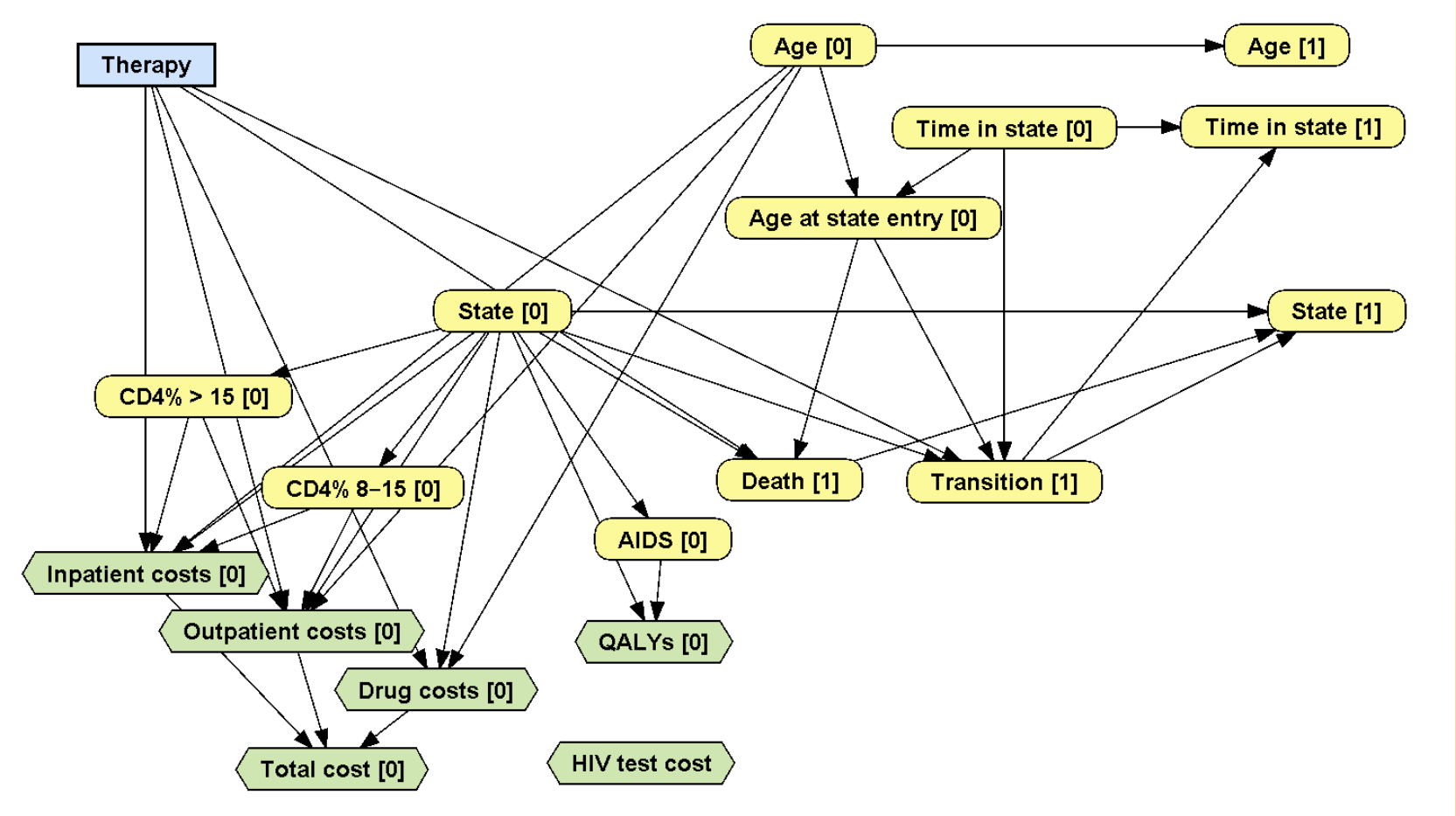
Objective: To assess the cost-effectiveness of cotrimoxazole prophylaxis in HIV-infected children in Zambia, as implementation at the local health centre level has yet to be undertaken in many resource-limited countries despite recommendations in recent updated World Health Organization (WHO) guidelines.

Design: A probabilistic decision analytical model of HIV/AIDS progression in children based on the CD4 cell percentage (CD4%) was populated with data from the placebo-controlled Children with HIV Antibiotic Prophylaxis trial that had reported a 43% reduction in mortality with cotrimoxazole prophylaxis in HIV-infected children aged 1–14 years.

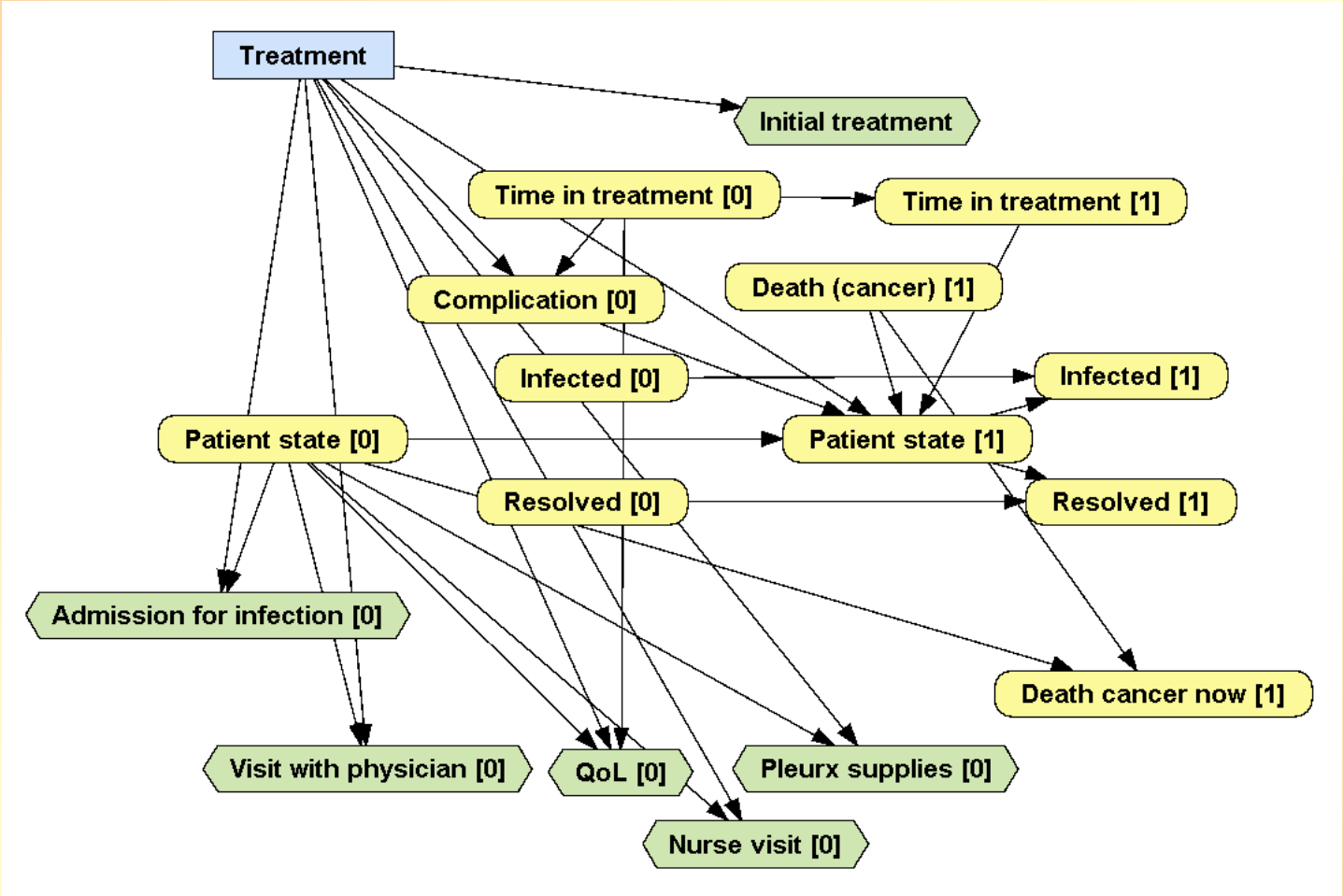
Methods: Unit costs (US$ in 2006) were measured at University Teaching Hospital, Lusaka. Cost-effectiveness expressed as cost per life-year saved, cost per quality adjusted life-year (QALY) saved, cost per disability adjusted life-year (DALY) averted was calculated across a number of different scenarios at tertiary and primary healthcare centres

A MID version of the CHAP model

[Ryan et al., 2008]

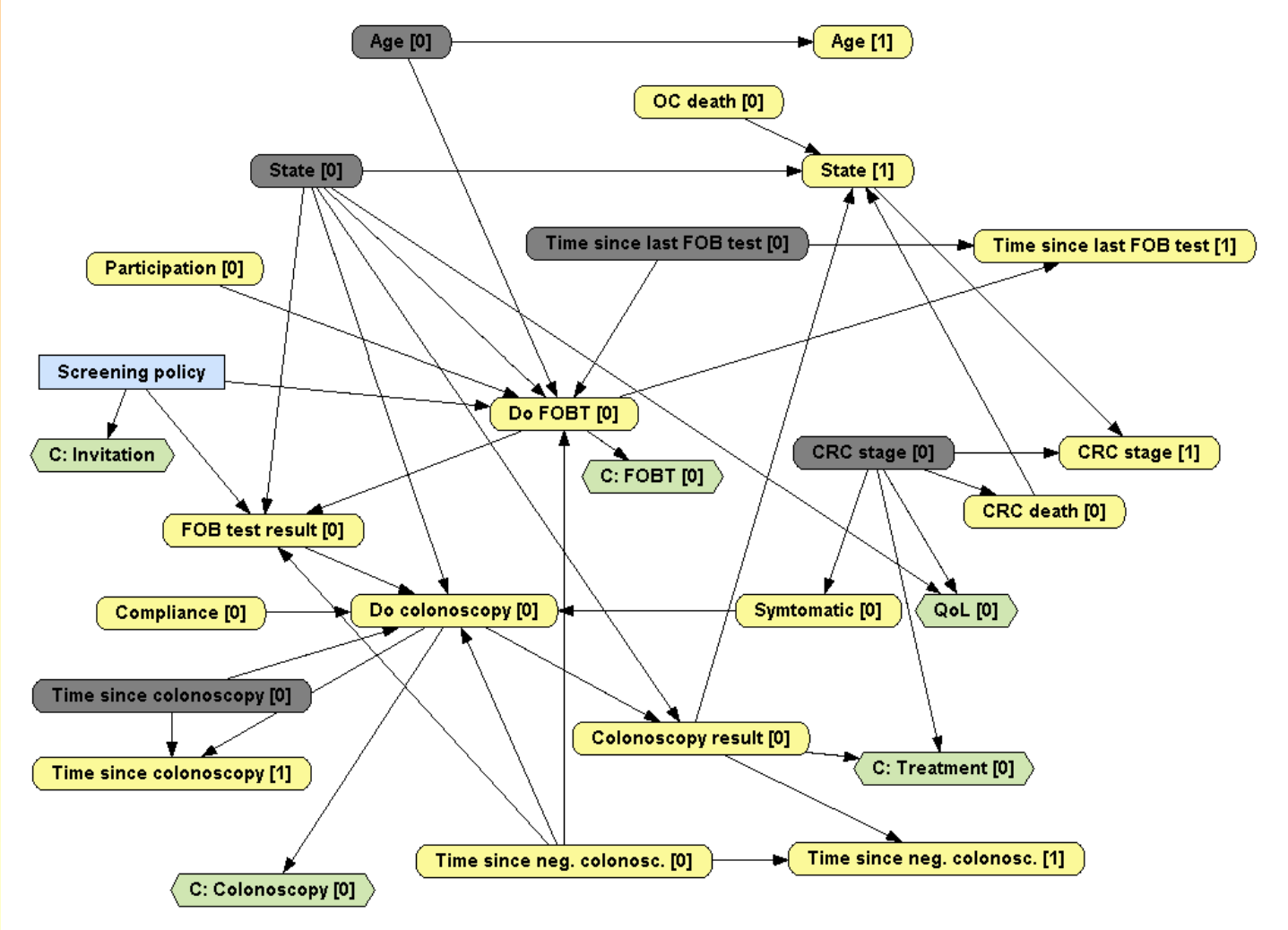


Our model for malignant pleural effusion



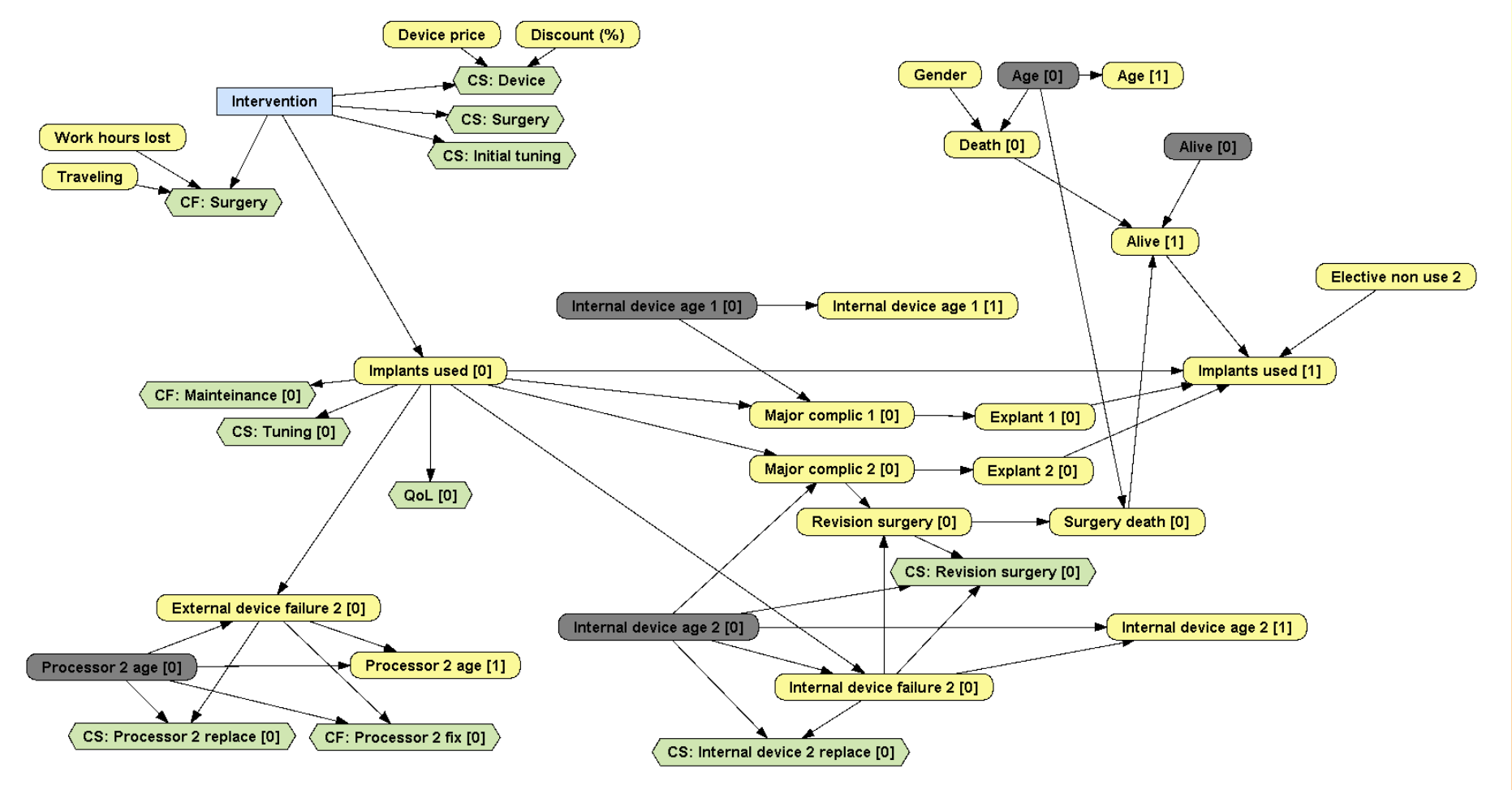
- *Meeting of the Society for Medical Decision Making (SMDM 2015)*, St. Louis, October 2015.

Our model for colorectal cancer screening



- *European Conference of the Society for Medical Decision Making*, London, UK, June 2015.

Our model for bilateral cochlear implantation



- *Cochlear Implant Symposium*, Washington DC, October 2015.

ORIGINAL ARTICLE

Cost-effectiveness of cardiovascular magnetic resonance in the diagnosis of coronary heart disease: an economic evaluation using data from the CE-MARC study

Simon Walker,[1] François Girardin,[1,2,3] Claire McKenna,[1] Stephen G Ball,[4] Jane Nixon,[5] Sven Plein,[4] John P Greenwood,[4] Mark Sculpher[1]

▸ Additional material is published online only. To view please visit the journal online (http://dx.doi.org/10.1136/heartjnl-2013-303624).

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Received 10 January 2013
Revised 15 March 2013
Accepted 17 March 2013

ABSTRACT

Objective To evaluate the cost-effectiveness of diagnostic strategies for coronary heart disease (CHD) derived from the CE-MARC study.

Design Cost-effectiveness analysis using a decision analytic model to compare eight strategies for the diagnosis of CHD.

Setting Secondary care out-patients (Cardiology Department).

Patients Patients referred to cardiologists for the further evaluation of symptoms thought to be angina pectoris.

Interventions Eight different strategies were considered, including different combinations of exercise treadmill testing (ETT), single-photon emission CT (SPECT), cardiovascular magnetic resonance (CMR) and coronary angiography (CA).

Main outcome measures Costs expressed as UK sterling in 2010–2011 prices and health outcomes in quality-adjusted life-years (QALYs). The time horizon was 50 years.

Results Based on the characteristics of patients in the CE-MARC study, only two strategies appear potentially cost-effective for diagnosis of CHD, both including CMR. The choice is between two strategies: one in which CMR follows a positive or inconclusive ETT, followed by CA if CMR is positive or inconclusive (Strategy 3 in the model); and the other where CMR is followed by CA if

INTRODUCTION

Coronary heart disease (CHD) is a leading cause of death and disability worldwide. In the UK, over 2 million people are living with CHD and, in 2007, it was estimated to account for over 94 000 deaths, of which over 31 000 were considered premature.[1]

A variety of investigations may be used to diagnose CHD and identify patients who require coronary revascularisation; all these tests, however, have their limitations. Increasingly, non-invasive imaging has replaced exercise treadmill testing (ETT), with single-photon emission CT (SPECT) being the most commonly used test for myocardial ischaemia worldwide.[2] Cardiovascular magnetic resonance (CMR) imaging is increasingly used for the diagnosis of CHD as a result of its safety (no ionising radiation), high spatial resolution and ability to assess multiple aspects of CHD pathology in both the stable and unstable clinical settings.[3–8]

The diagnosis of CHD has no direct health benefit in itself; instead, any improved accuracy in diagnosis should result in more appropriate treatment which can confer health benefits on patients. The optimal management of patients with CHD continues to be debated, but options include medical therapy, percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG). Many patients with

Model structure

To conduct the economic evaluation a decision analytic model was developed. For the initial diagnosis a decision tree allocates patients to the appropriate diagnostic group. The prognostic implications of being in one of these groups are then quantified using three distinct Markov models. An example of the decision tree for Strategy 2 (ETT, followed by CA if ETT is positive or inconclusive) is shown in figure 1.

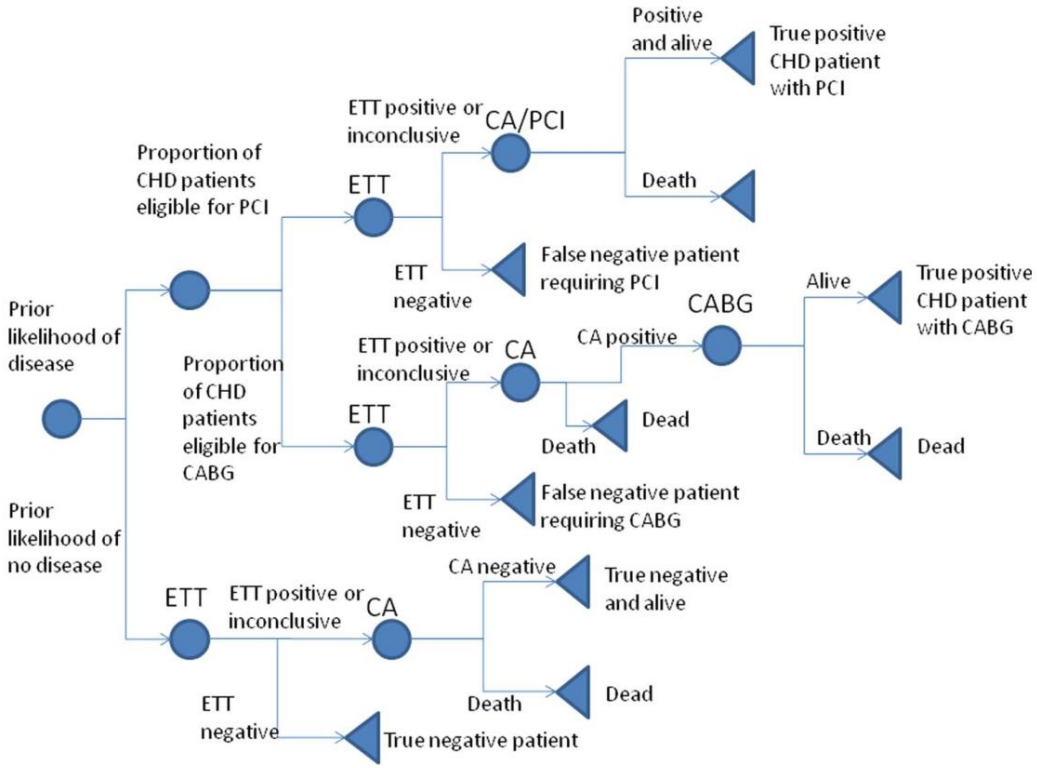
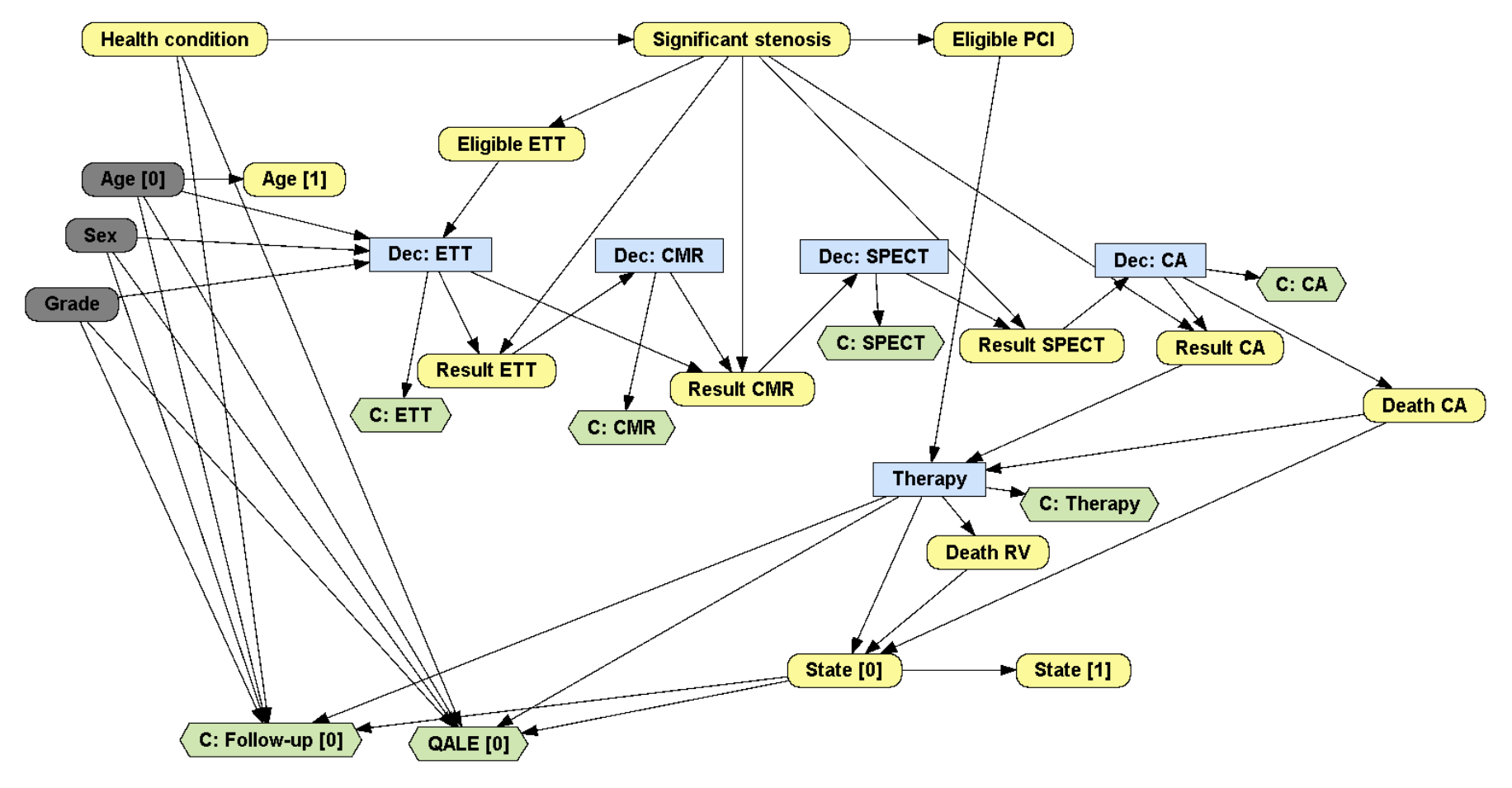


Figure 1 Structure of decision tree using Strategy 2 as an example. CA, coronary angiography; CABG, coronary artery bypass grafting; CHD, coronary heart disease; ETT, exercise treadmill testing; PCI, percutaneous coronary intervention.

A MID with several decisions

Adapted from [Walker et al., 2013]



- This model evaluates all the possible interventions.
- It can cope with heterogeneity: sex, age, grade.

PharmacoEconomics (2017) 35:817–830
DOI 10.1007/s40273-017-0510-8

REVIEW ARTICLE

A Comparison of Four Software Programs for Implementing Decision Analytic Cost-Effectiveness Models

Chase Hollman[1] · Mike Paulden[1,2] · Petros Pechlivanoglou[3,4,5] · Christopher McCabe[1]

Published online: 9 May 2017

Abstract The volume and technical complexity of both academic and commercial research using decision analytic modelling has increased rapidly over the last two decades. The range of software programs used for their implementation has also increased, but it remains true that a small number of programs account for the vast majority of cost-effectiveness modelling work. We report a comparison of four software programs: TreeAge Pro, Microsoft Excel, R and MATLAB. Our focus is on software commonly used for building Markov models and decision trees to conduct cohort simulations, given their predominance in the published literature around cost-effectiveness modelling. Our comparison uses three qualitative criteria as proposed by Eddy et al.: "transparency and validation", "learning curve" and "capability". In addition, we introduce the quantitative criterion of processing speed. We also consider the cost of each program to academic users and commercial users. We rank the programs based on each of these criteria. We find that, whilst Microsoft Excel and TreeAge Pro are good programs for educational purposes and for producing the types of analyses typically required by health technology assessment agencies, the efficiency and transparency advantages of programming languages such as MATLAB and R become increasingly valuable when more complex analyses are required.

Key Points for Decision Makers

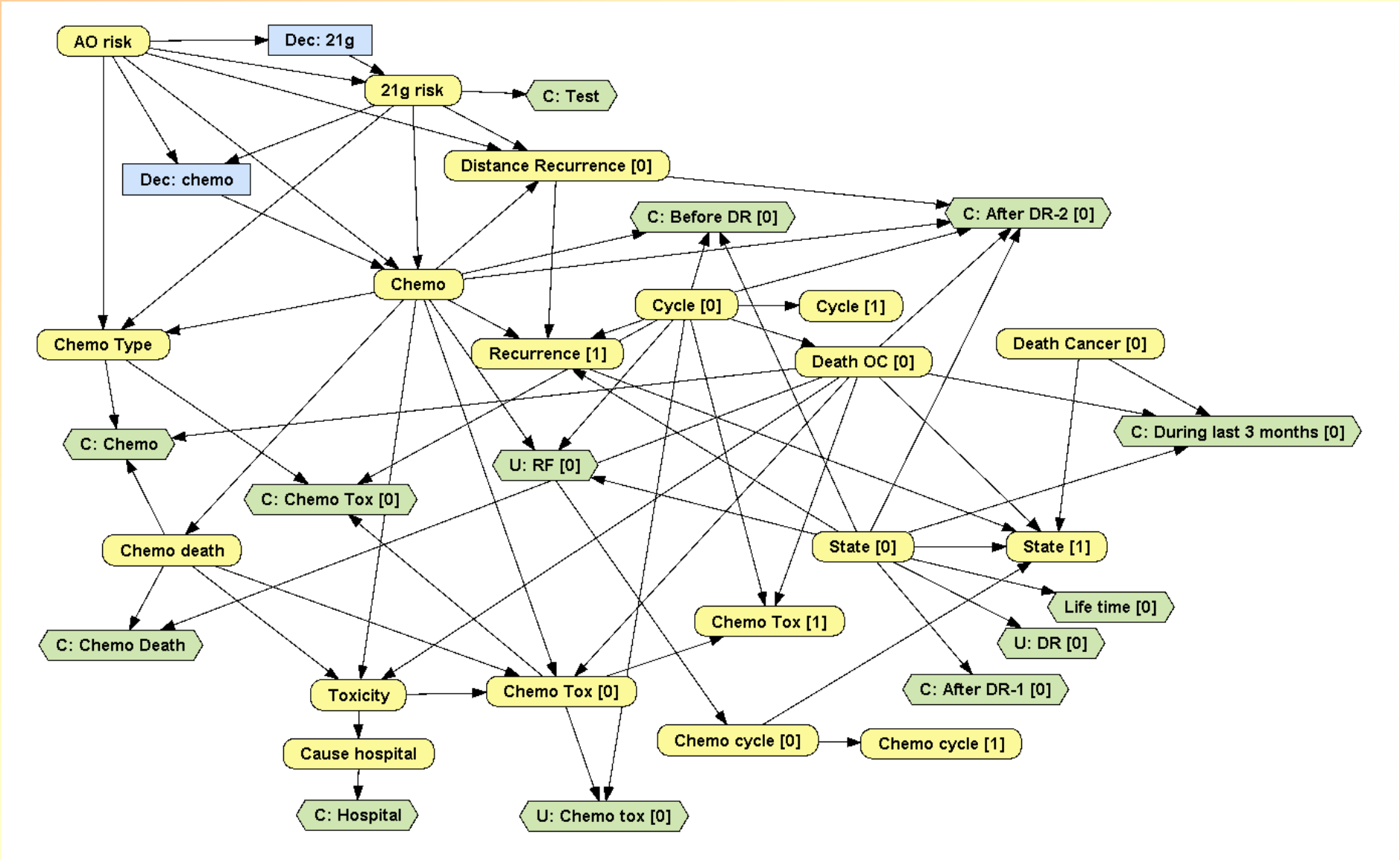
Microsoft Excel and TreeAge Pro are good programs for implementing the types of cost-effectiveness analyses commonly required by health technology assessment bodies.

MATLAB and R are particularly valuable for implementing more complex decision analytic models and computationally demanding analyses, such as expected value of perfect parameter information (EVPPI), due to their processing speed and transparency.

Electronic supplementary material The online version of this article (doi:10.1007/s40273-017-0510-8) contains supplementary material, which is available to authorized users.

✉ Mike Paulden
paulden@ualberta.ca

MID version of the 21-gene model



6.2.3. Half-cycle correction

Medical Decision Making 2016;36:115-131

ORIGINAL ARTICLE

Theoretical Foundations and Practical Applications of Within-Cycle Correction Methods

Elamin H. Elbasha, PhD, Jagpreet Chhatwal, PhD

Background. *Modeling guidelines recommend applying a half-cycle correction (HCC) to outcomes from discrete-time state-transition models (DTSTMs). However, there is still no consensus on why and how to perform the correction. The objective was to provide theoretical foundations for HCC and to compare (both mathematically and numerically) the performance of different correction methods in reducing errors in outcomes from DTSTMs.* ***Methods***. *We defined 7 methods from the field of numerical integration: Riemann sum of rectangles (left, midpoint, right), trapezoids, life-table, and Simpson's 1/3rd and 3/8th rules. We applied these methods to a standard 3-state disease progression Markov chain to evaluate the cost-effectiveness of a hypothetical intervention. We solved the discrete- and continuous-time (our gold standard) versions of the model analytically and derived expressions for various outcomes including discounted quality-adjusted life-years, discounted costs, and incremental cost-effectiveness ratios.* ***Results***. *The standard HCC method gave the same results as the trapezoidal rule and life-table method. We found situations where applying the standard HCC can do more harm than good. Compared with the gold standard, all correction methods resulted in approximation errors. Contrary to conventional wisdom, the errors need not cancel each other out or become insignificant when incremental outcomes are calculated. We found that a wrong decision can be made with a less accurate method. The performance of each correction method vastly improved when a shorter cycle length was selected; Simpson's 1/3rd rule was the fastest method to converge to the gold standard.* ***Conclusion***. *Cumulative outcomes in DTSTMs are prone to errors that can be reduced with more accurate methods like Simpson's rules. We clarified several misconceptions and provided recommendations and algorithms for practical implementation of these methods.* ***Key words:*** *state-transition models; discrete time; continuous time; half-cycle correction; numerical integration.* ***(Med Decis Making XXXX;XX:XX–XX)***

Within-cycle correction methods

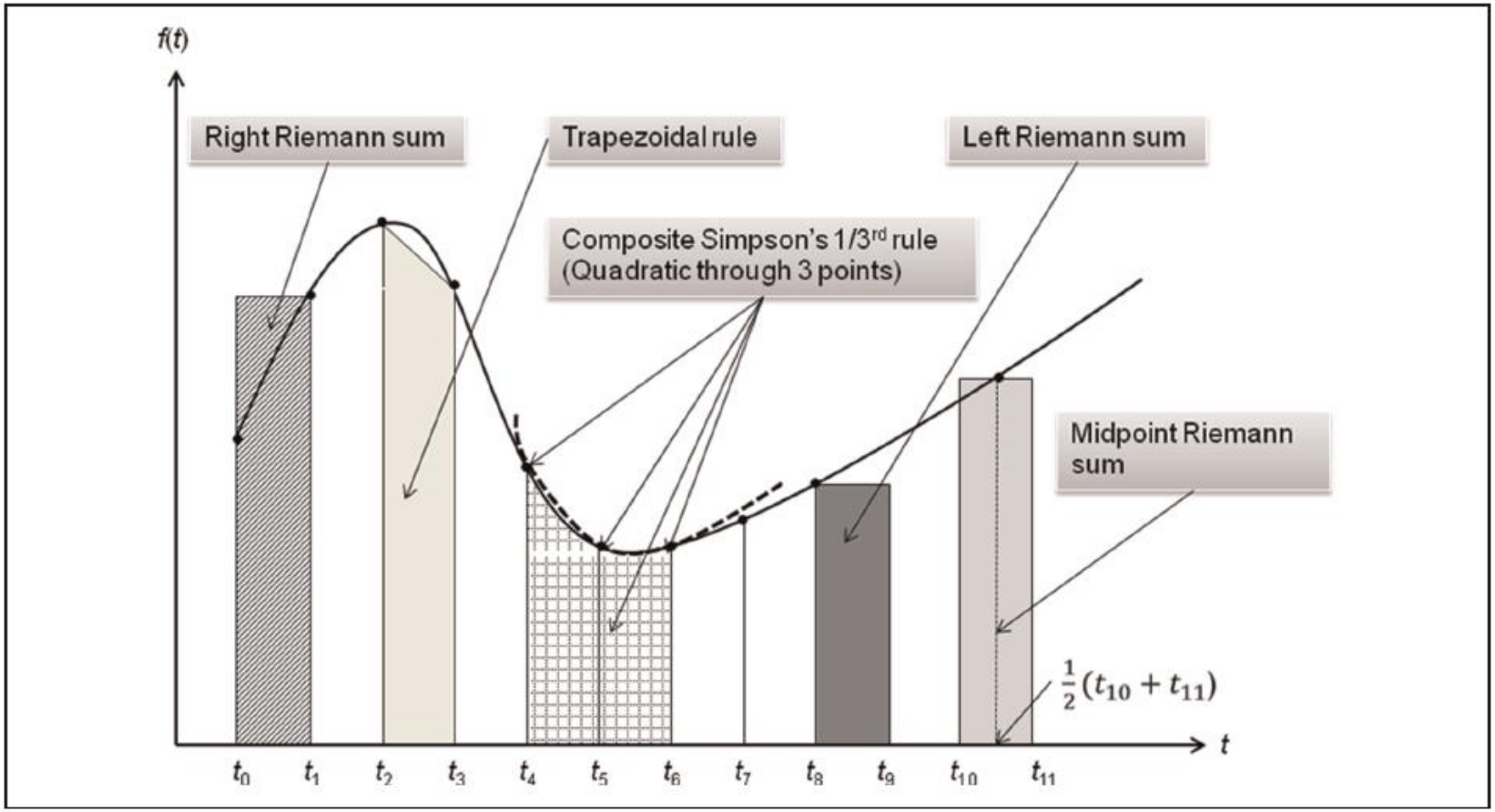


Figure 1 Geometric illustration of the Riemann sums, trapezoidal rule, and composite Simpson's rules.

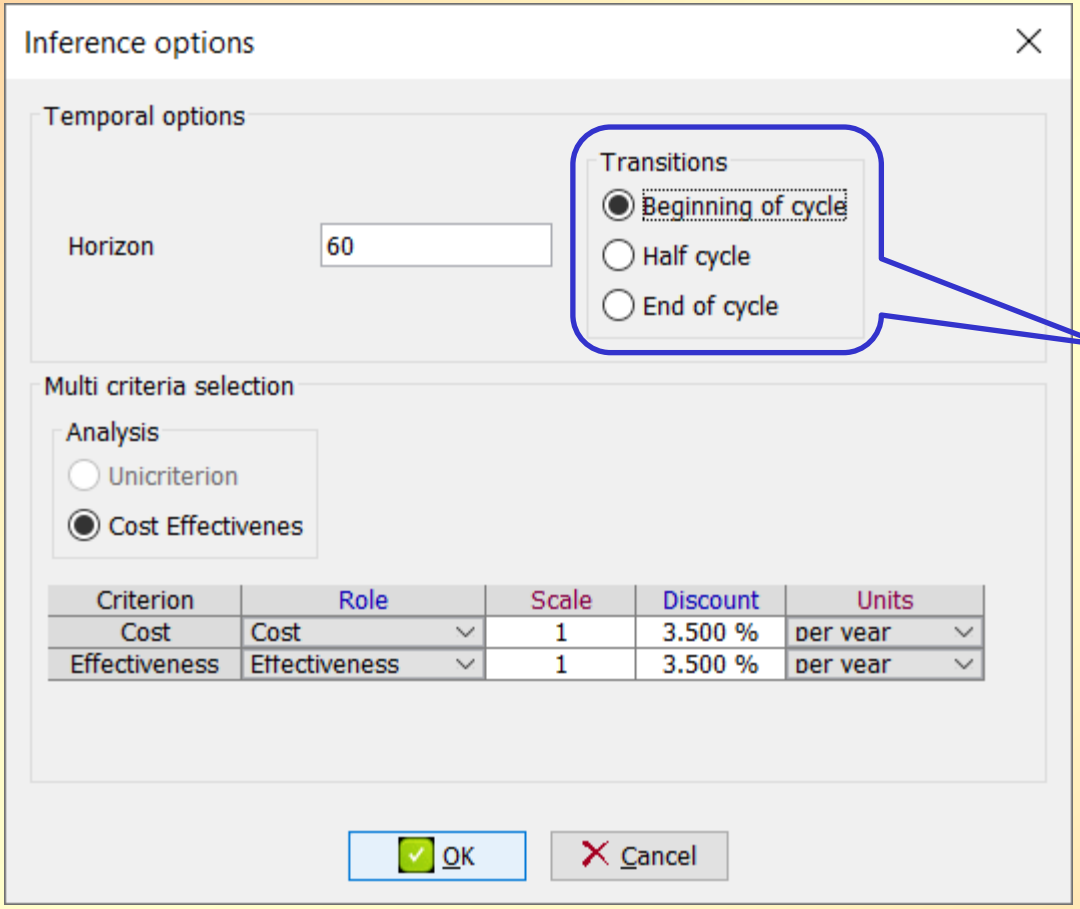
[Elbasha and Chhatwal, 2016]

Table 4 Formulas for State Membership per Cycle and Cumulative Outcomes with Different Methods for Discrete-Time, State-Transition Model

Outcome[a]	Formula
Persons well	$W_k = w_0[1-(1-e)b-m]^{\frac{k}{n}}$
Persons with disease	$S_k = \frac{[b(1-e)-(d-m)(1-w_0)](1-d)^{\frac{k}{n}} - w_0 b(1-e)[1-(1-e)b-m]^{\frac{k}{n}}}{b(1-e)+m-d}$
Cases of death	$D_k = \frac{[b(1-e)-(d-m)(1-w_0)]\left[1-(1-d)^k\right] - w_0(d-m)\left\{1-[1-(1-e)b-m]^k\right\}}{b(1-e)+m-d}$
Risk of disease over T years	
Right Riemann sum	$RISK_R = \frac{b(1-e)\left\{1-[1-(1-e)b-m]^T\right\}w_0\left\{(1-d)^{\frac{1}{n}}-[1-(1-e)b-m]^{\frac{1}{n}}\right\}}{[b(1-e)+m-d]\left\{1-[1-(1-e)b-m]^{-\frac{1}{n}}\right\}}$
Trapezoidal rule	$RISK_Z = RISK_R + \frac{b(1-e)\left\{1-[1-(1-e)b-m]^T\right\}w_0\left\{(1-d)^{\frac{1}{n}}-[1-(1-e)b-m]^{\frac{1}{n}}\right\}}{2[b(1-e)+m-d]}$
Simpson's 1/3rd rule	$RISK_C = b(1-e)w_0\left\{(1-d)^{\frac{1}{n}}-[1-(1-e)b-m]^{\frac{1}{n}}\right\} \times \frac{\left[1+4[1-b(1-e)-m]^{\frac{1}{n}}+[1-b(1-e)-m]^{\frac{2}{n}}\right]\left\{1-[1-(1-e)b-m]^T\right\}}{3[b(1-e)+m-d]\left\{1-[1-b(1-e)-m]^{\frac{2}{n}}\right\}}$
Simpson's 3/8th rule	$RISK_{CR} = \frac{3b(1-e)w_0\left\{(1-d)^{\frac{1}{n}}-[1-(1-e)b-m]^{\frac{1}{n}}\right\}\left[1+[1-b(1-e)-m]^{\frac{1}{n}}\right]^3\left\{1-[1-(1-e)b-m]^T\right\}}{8[b(1-e)+m-d]\left\{1-[1-b(1-e)-m]^{\frac{3}{n}}\right\}}$
Discounted QALYs (years)	
Right Riemann sum	$QALY_R = \frac{w_0[b(1-e)(u-q)-(d-m)u]\left\{1-\left[\frac{1-(1-e)b-m}{1+r}\right]^T\right\}}{n[b(1-e)+m-d]\left\{\left[\frac{1-(1-e)b-m}{1+r}\right]^{-\frac{1}{n}}-1\right\}} + \frac{q[b(1-e)-(d-m)(1-w_0)]\left[1-\left(\frac{1-d}{1+r}\right)^T\right]}{n[b(1-e)+m-d]\left[\left(\frac{1-d}{1+r}\right)^{-\frac{1}{n}}-1\right]}$
Trapezoidal rule	$QALY_Z = QALY_R(e) + \frac{w_0[b(1-e)(u-q)-(d-m)u]\left\{1-\left[\frac{1-(1-e)b-m}{1+r}\right]^T\right\}}{2n[b(1-e)+m-d]} + \frac{q[b(1-e)-(d-m)(1-w_0)]\left[1-\left(\frac{1-d}{1+r}\right)^T\right]}{2n[b(1-e)+m-d]}$
Simpson's 1/3rd rule	$QALY_C = \frac{q[b(1-e)-(d-m)(1-w_0)]\left[1+4\left(\frac{1-d}{1+r}\right)^{\frac{1}{n}}+\left(\frac{1-d}{1+r}\right)^{\frac{2}{n}}\right]\left[1-\left(\frac{1-d}{1+r}\right)^T\right]}{3n[b(1-e)+m-d]\left[1-\left(\frac{1-d}{1+r}\right)^{\frac{2}{n}}\right]} + \frac{w_0[b(1-e)(u-q)-(d-m)u]\left[1+4\left[\frac{1-b(1-e)-m}{1+r}\right]^{\frac{1}{n}}+\left[\frac{1-b(1-e)-m}{1+r}\right]^{\frac{2}{n}}\right]\left\{1-\left[\frac{1-(1-e)b-m}{1+r}\right]^T\right\}}{3n[b(1-e)+m-d]\left\{1-\left[\frac{1-b(1-e)-m}{1+r}\right]^{\frac{2}{n}}\right\}}$
Simpson's 3/8th rule	$QALY_{CR} = \frac{3q[b(1-e)-(d-m)(1-w_0)]\left[1+\left(\frac{1-d}{1+r}\right)^{\frac{1}{n}}\right]^3\left[1-\left(\frac{1-d}{1+r}\right)^T\right]}{8n[b(1-e)+m-d]\left[1-\left(\frac{1-d}{1+r}\right)^{\frac{3}{n}}\right]} + \frac{3w_0[b(1-e)(u-q)-(d-m)u]\left[1+\left[\frac{1-b(1-e)-m}{1+r}\right]^{\frac{1}{n}}\right]^3\left\{1-\left[\frac{1-(1-e)b-m}{1+r}\right]^T\right\}}{8n[b(1-e)+m-d]\left\{1-\left[\frac{1-b(1-e)-m}{1+r}\right]^{\frac{3}{n}}\right\}}$
Discounted disease costs	
Right Riemann sum	$COST_R = \frac{cw_0b(1-e)\left[1-\left(\frac{1-(1-e)b-m}{1+r}\right)^T\right]}{n[b(1-e)+m-d]\left\{1-\left[\frac{1-(1-e)b-m}{1+r}\right]^{-\frac{1}{n}}\right\}} + \frac{c[b(1-e)-(d-m)(1-w_0)]\left[1-\left(\frac{1-d}{1+r}\right)^T\right]}{n[b(1-e)+m-d]\left[\left(\frac{1-d}{1+r}\right)^{-\frac{1}{n}}-1\right]}$
Trapezoidal rule	$COST_Z = COST_R - \frac{cw_0b(1-e)\left[1-\left(\frac{1-(1-e)b-m}{1+r}\right)^T\right]}{2n[b(1-e)+m-d]} + \frac{c[b(1-e)-(d-m)(1-w_0)]\left[1-\left(\frac{1-d}{1+r}\right)^T\right]}{2n[b(1-e)+m-d]}$
Simpson's 1/3rd rule	$COST_C = \frac{c[b(1-e)-(d-m)(1-w_0)]\left[1+4\left(\frac{1-d}{1+r}\right)^{\frac{1}{n}}+\left(\frac{1-d}{1+r}\right)^{\frac{2}{n}}\right]\left[1-\left(\frac{1-d}{1+r}\right)^T\right]}{3n[b(1-e)+m-d]\left[1-\left(\frac{1-d}{1+r}\right)^{\frac{2}{n}}\right]} - \frac{cw_0b(1-e)\left[1+4\left[\frac{1-b(1-e)-m}{1+r}\right]^{\frac{1}{n}}+\left[\frac{1-b(1-e)-m}{1+r}\right]^{\frac{2}{n}}\right]\left\{1-\left[\frac{1-(1-e)b-m}{1+r}\right]^T\right\}}{3n[b(1-e)+m-d]\left\{1-\left[\frac{1-b(1-e)-m}{1+r}\right]^{\frac{2}{n}}\right\}}$
Simpson's 3/8th rule	$COST_{CR} = \frac{3c[b(1-e)-(d-m)(1-w_0)]\left[1+\left(\frac{1-d}{1+r}\right)^{\frac{1}{n}}\right]^3\left[1-\left(\frac{1-d}{1+r}\right)^T\right]}{8n[b(1-e)+m-d]\left[1-\left(\frac{1-d}{1+r}\right)^{\frac{3}{n}}\right]} - \frac{3cw_0b(1-e)\left[1+\left[\frac{1-b(1-e)-m}{1+r}\right]^{\frac{1}{n}}\right]^3\left\{1-\left[\frac{1-(1-e)b-m}{1+r}\right]^T\right\}}{8n[b(1-e)+m-d]\left\{1-\left[\frac{1-b(1-e)-m}{1+r}\right]^{\frac{3}{n}}\right\}}$
Net monetary benefits	
Method x (R, Z, C, CR)	$NMB_x = \lambda QALY_x - COST_x - I$

Note: b = transition probability to the Disease state; c = disease cost per period; C = Simpson's 1/3rd rule; COST = discounted cost of disease; CR = Simpson's 3/8th rule; d = transition probability to the Dead state from the Disease state; D_k = persons in the Dead state; e = probability of intervention reducing disease progression; I = intervention cost; m = probability of all-cause death for well persons; NMB = net monetary benefits; q = quality of life loss; QALY = quality-adjusted life-years; r = discount rate; R = right Riemann; RISK = cumulative risk of disease; S_k = persons in the Disease state; T = time horizon; w_0 = proportion of the cohort initially in the Well state; W_k = persons in the Well state; Z = trapezoidal rule; λ = willingness-to-pay for a QALY.
a. Outcomes in the absence of the intervention are obtained by setting $e = I = 0$.

“Within-cycle corrections” in OpenMarkov



This will change in future versions of OpenMarkov: replaced with properly computed “within-cycle corrections”:

- beginning of cyle
- half cycle
- end of cycle
- Simpson’s 1/3 rule
- Simpson’s 3/8 rule

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Evaluation of Markov Models with Discontinuities.

Pérez-Martín J[1], Bermejo I, Díez FJ[1].

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Abstract

Background. Several methods, such as the half-cycle correction and the life-table method, were developed to attenuate the error introduced in Markov models by the discretization of time. Elbasha and Chhatwal have proposed alternative "corrections" based on numerical integration techniques. They present an example whose results suggest that the trapezoidal rule, which is equivalent to the half-cycle correction, is not as accurate as Simpson's 1/3 and 3/8 rules. However, they did not take into consideration the impact of discontinuities. **Objective**. To propose a method for evaluating Markov models with discontinuities. **Design**. Applying the trapezoidal rule, we derive a method that consists of adjusting the model by setting the cost at each point of discontinuity to the mean of the left and right limits of the cost function. We then take from the literature a model with a cycle length of 1 year and a discontinuity on the cost function and compare our method with other "corrections" using as the gold standard an equivalent model with a cycle length of 1 day. **Results**. As expected, for this model, the life-table method is more accurate than assuming that transitions occur at the beginning or the end of cycles. The application of numerical integration techniques without taking into account the discontinuity causes large errors. The model with averaged cost values yields very small errors, especially for the trapezoidal and the 1/3 Simpson rules. **Conclusion**. In the case of discontinuities, we recommend applying the trapezoidal rule on an averaged model because this method has a mathematical justification, and in our empirical evaluation, it was more accurate than the sophisticated 3/8 Simpson rule.

KEYWORDS: Markov models; discontinuities; half-cycle correction; state-transition models; within-cycle correction

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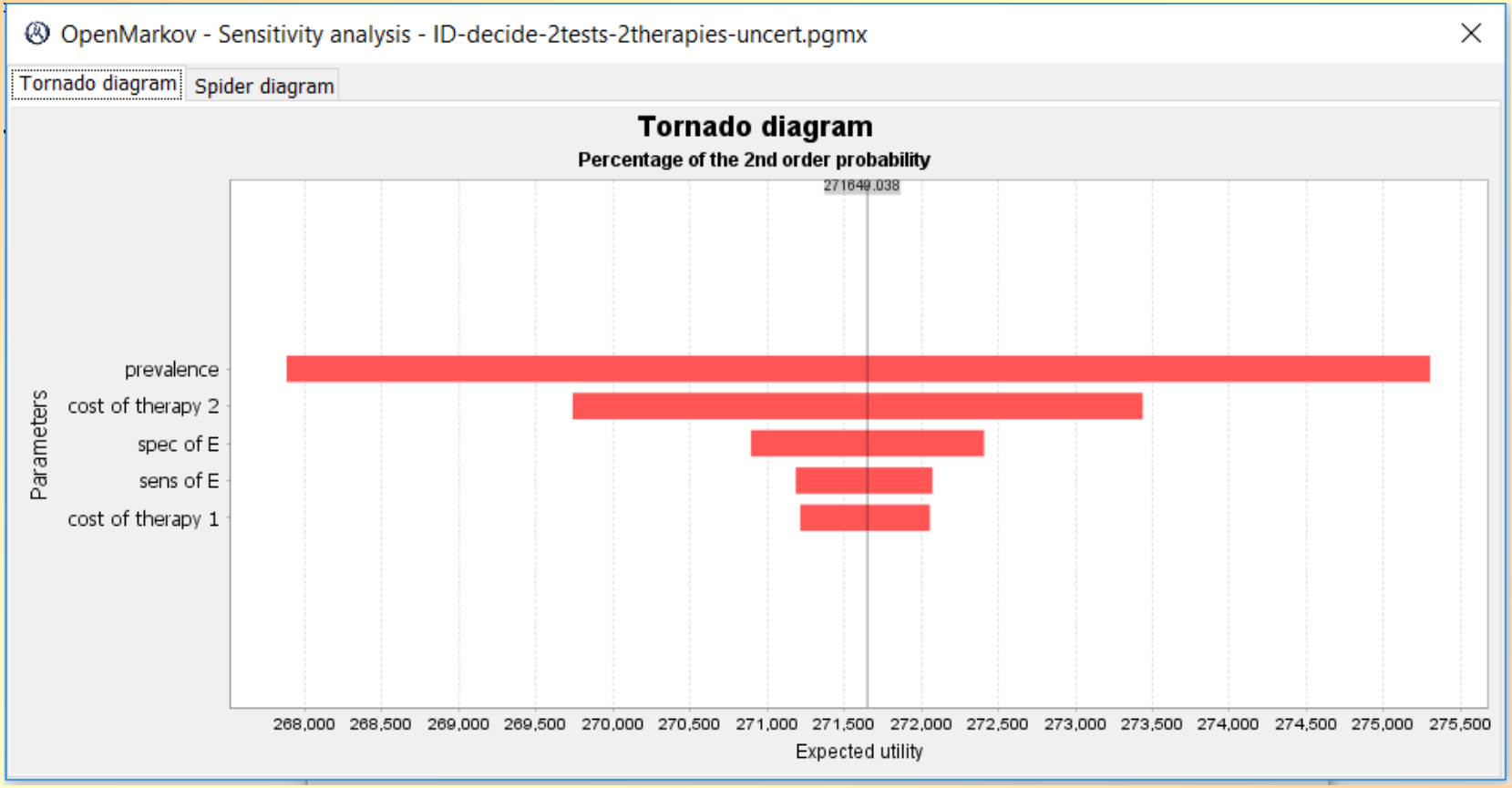
7. Sensitivity analysis

Types of sensitivity analysis

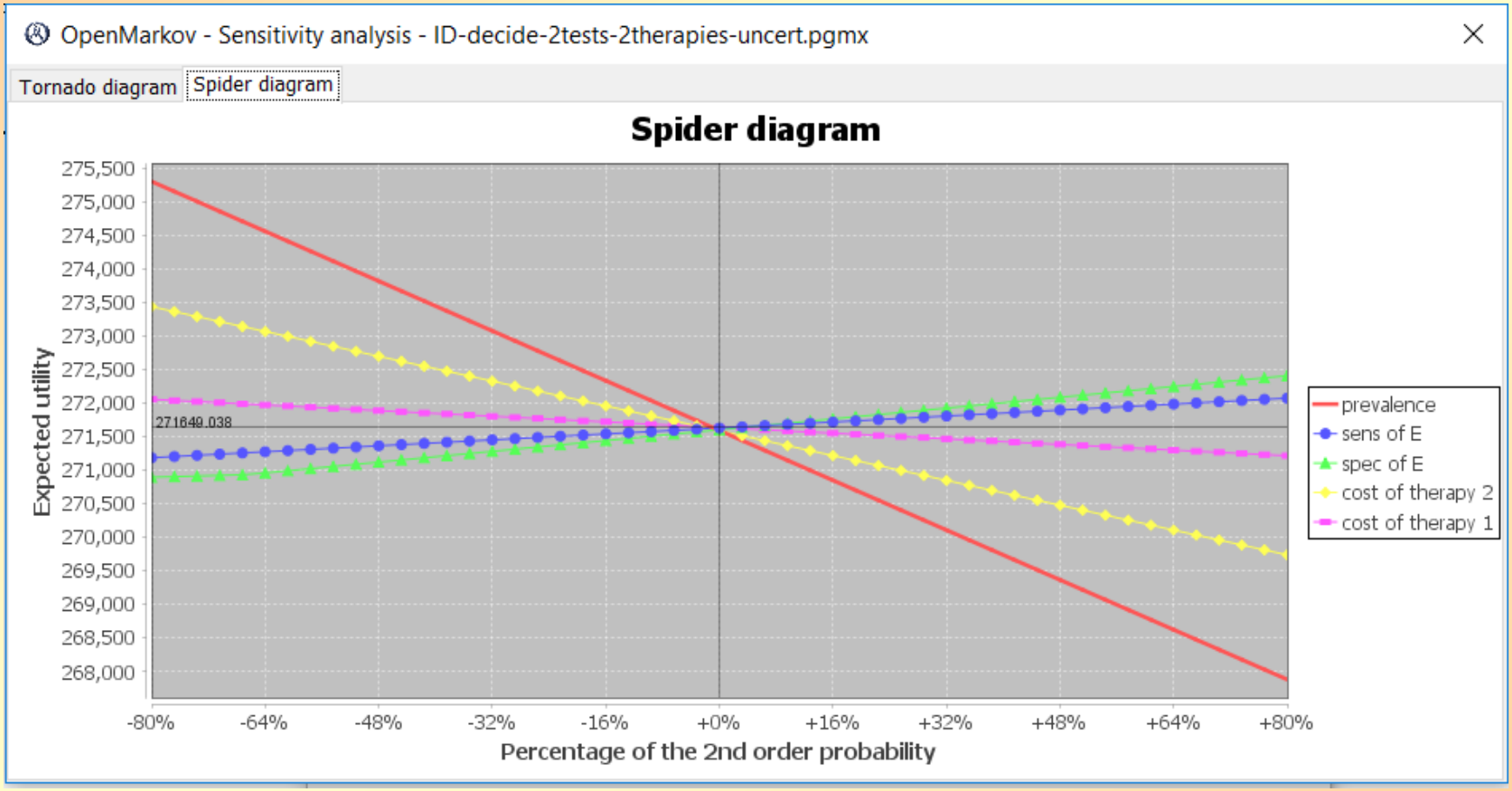
- Two main types
  - structural (qualitative)
  - parametric (quantitative)
- Depending on the effect analyzed
  - analysis of utility
  - analysis of decisions / policies
- Depending on how many parameters are varied
  - one-way analysis
  - *n*-way analysis (independent or join analysis)
- Depending on how the parameters are varied
  - range (interval)
  - probability distribution
  - look for thresholds (changes in policies)

7.1. Unicriterion sensitivity analysis

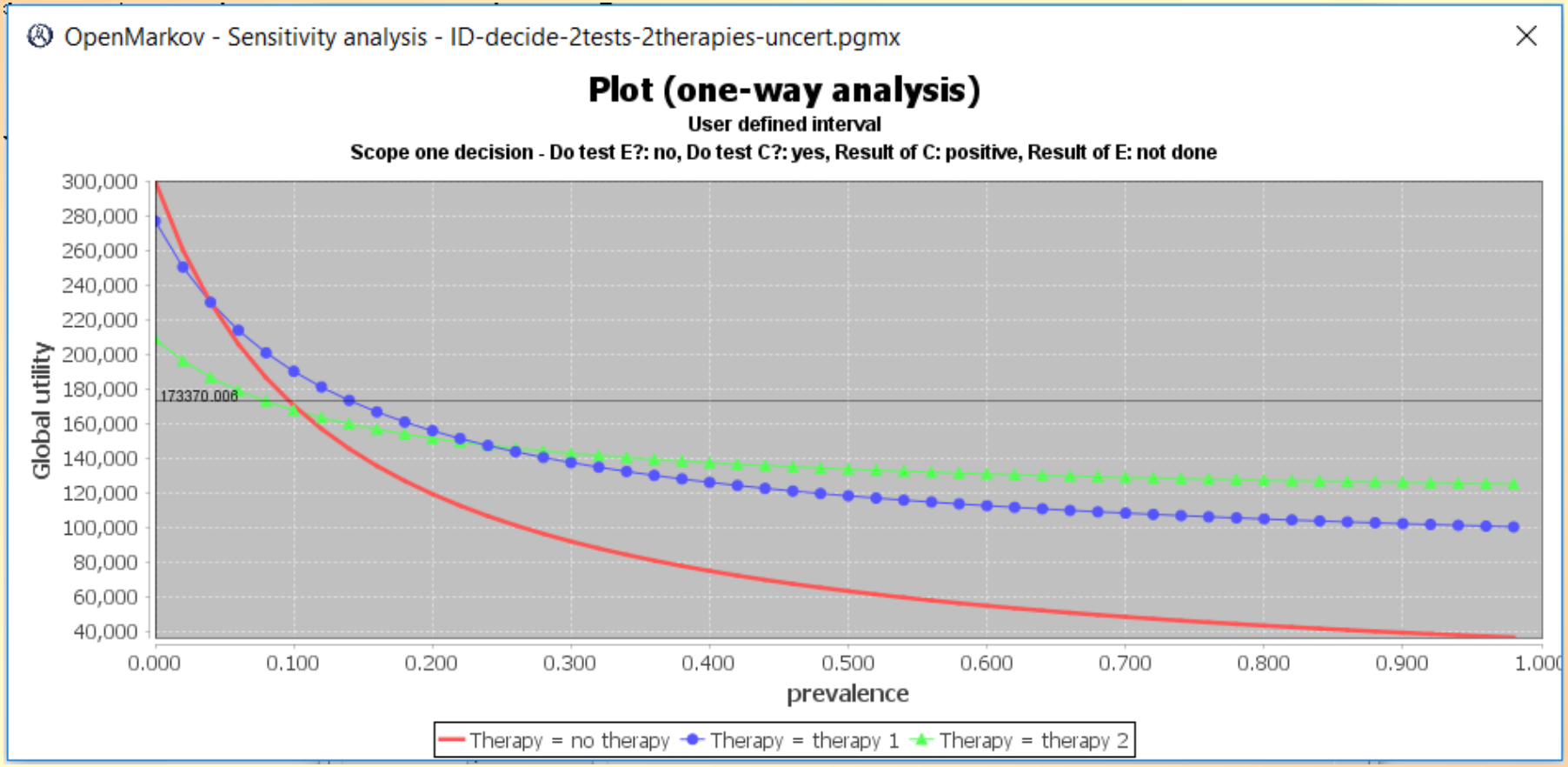
Tornado diagram



Spider diagram

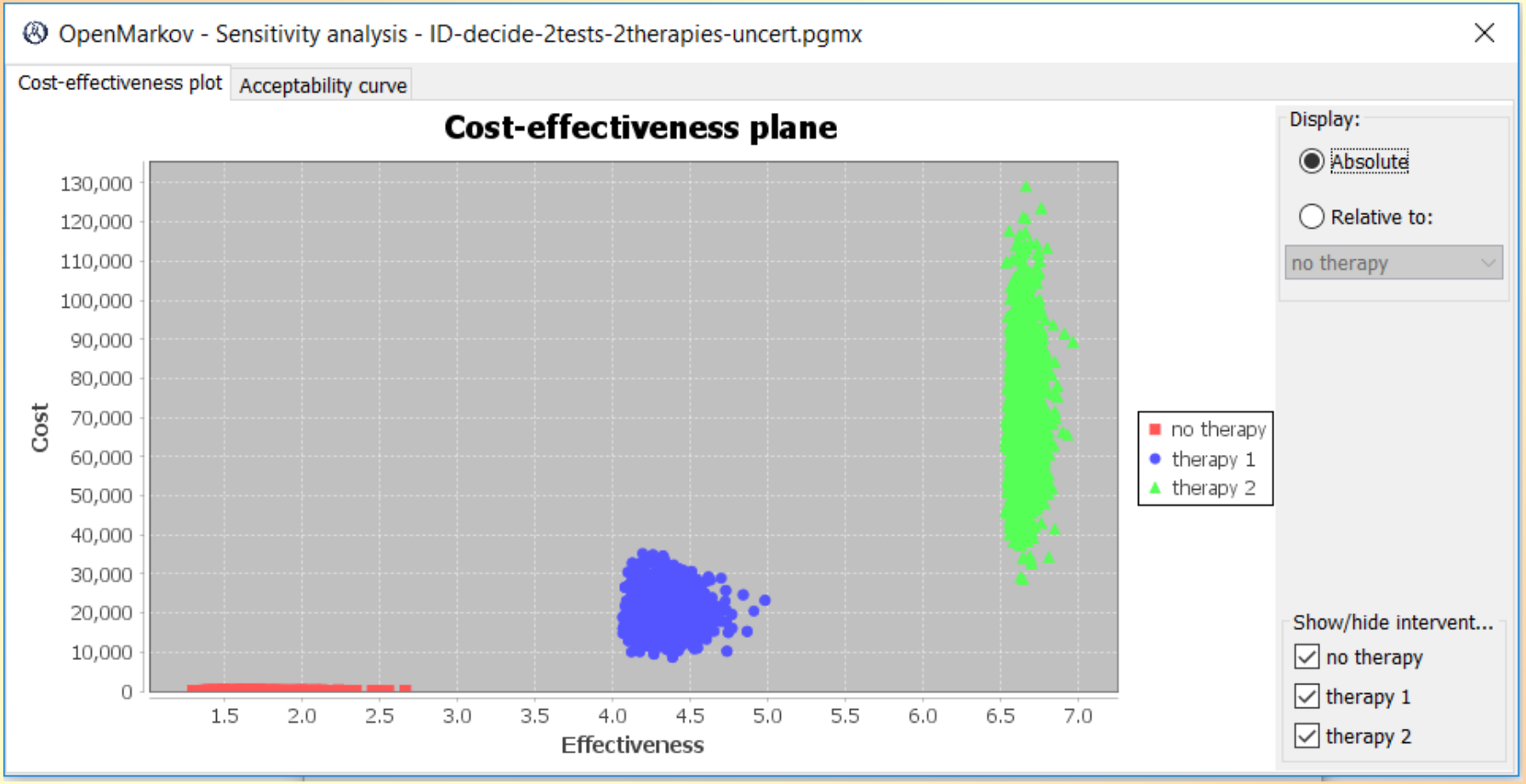


Plot (one-way sensitivity analysis)

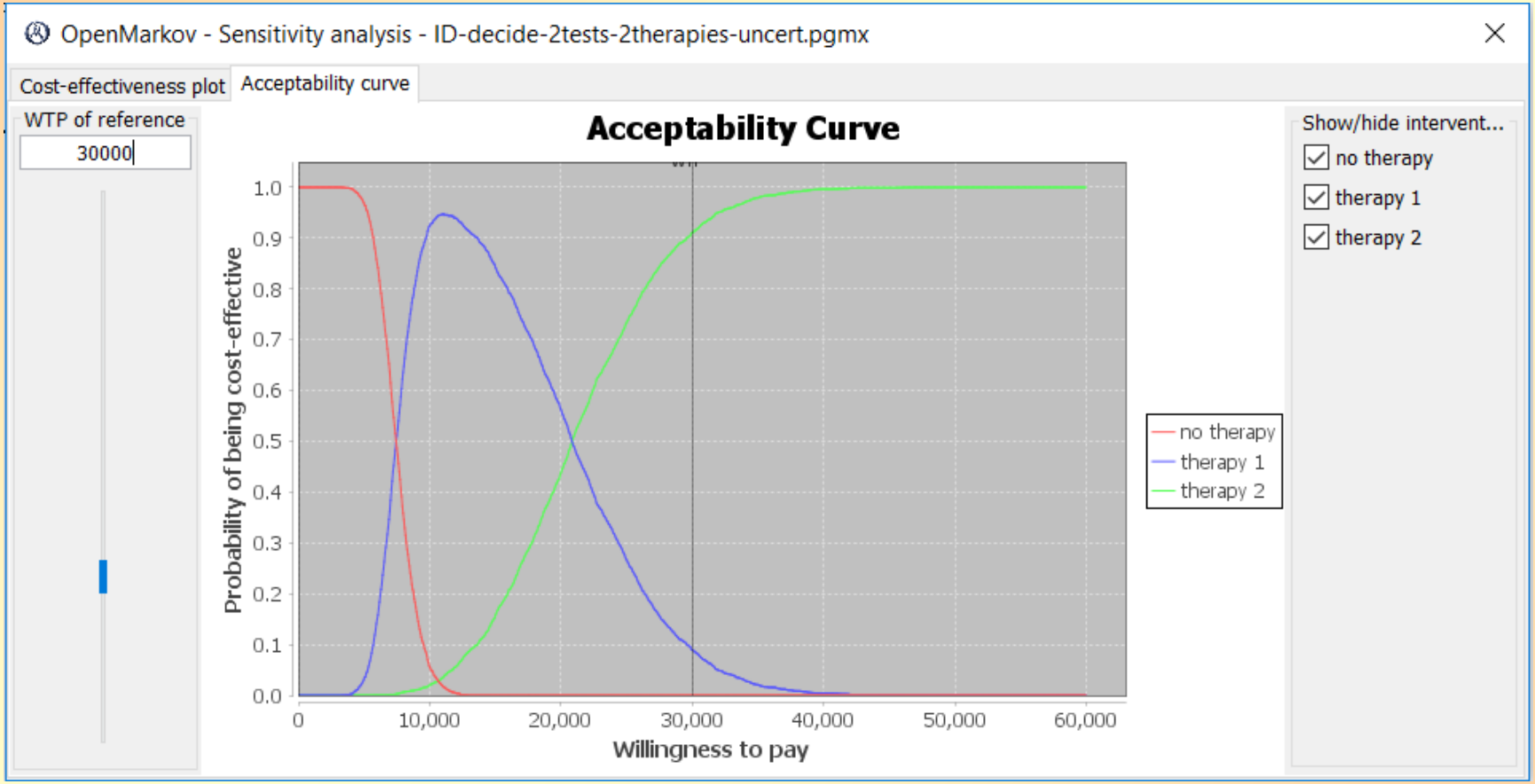


7.2. Cost-effectiveness sensitivity analysis

Scatter plot



Acceptability curve



Some sensitivity analysis options

	unicriterion	cost-effectiveness
deterministic	• tornado / spider diagram (global) • plot (global / for a decision) • map (global / for a decision)	• C.E. spider diagram (global)
probabilistic	• acceptability (for a decision) • EVPI (global)	• scatter plot + acceptability curve (for a decision) • EVPI curve (global)

Hands-on exercise 6

Uncertainty for the small Markov model

- Uncertainty about cost of new therapy
  - Gamma, with standard deviation = 20% of the mean
- Uncertainty about transition probabilities
  - one-month study: 400 volunteers with *latent* disease

Transition to ↓	**standard therapy**	**new therapy**
dead	4	4
active	22	16
latent (no transition)	174	180
TOTAL	200	200

- Questions
  - Prob. new therapy being cost-effective at WTP = $50,000/QALY
  - Prob. new therapy being effective (disregarding cost)

8. Overview of software tools

Software tools for CEA

REVIEW OF SOFTWARE FOR DECISION MODELLING.

DECISION SUPPORT UNIT

Jon Tosh and Allan Wailoo

Health Economics and Decision Science, School of Health and Related Research,

University of Sheffield

29 July 2008

Table 1 - Software used for NICE Technology Appraisals

Software	Respondents that used this software		Number of TAGs	Number of Manufacturers	Number of Consultancies
	n	%			
MS Excel	28	100%	6	14	8
TreeAge Pro	16	57%	6	7	3
WinBUGS	6	21%	1	2	3
R	5	18%	1	2	2
Arena	3	11%	0	2	1
SAS	3	11%	0	1	2
Crystal Ball	2	7%	1	0	1
Simu8	2	7%	1	0	1
STATA	1	4%	1	0	0
RevMAN	1	4%	1	0	0
Borland Delphi	1	4%	1	0	0
S-PLUS	1	4%	1	0	0
@risk	1	4%	0	0	1
STELLA	0	0%	0	0	0
Witness	0	0%	0	0	0

Software Packages for Graphical Models

Written by Kevin Murphy.
Last updated 16 June 2014.
(Thanks to Alex Gorban for helping me with the switch to Google Sheets.)

Review articles

- List of GM code at MLOSS
- Click here for a short article I wrote for the ISBA (International Society for Bayesian Analysis) Newsletter, December 2007, sumarizing some of the packages below.
- Click here for a more detailed discussion of some of these packages written by Ann Nicholson and Kevin Korb in 2004.
- Click here for a French version of my comparison table (not necessarily up-to-date).

What do the headers in the table mean?

- Src = source code included? (N=no) If so, what language?
- Cts = are continuous (latent) nodes supported? G = (conditionally) Gaussians nodes supported analytically, Cs = continuous nodes supported by sampling, Cd = continuous nodes supported by discretization, Cx = continuous nodes supported by some unspecified method, D = only discrete nodes supported.
- GUI = Graphical User Interface included?
- Learns parameters?
- Learns structure? CI = means uses conditional independency tests
- Utility = utility and decision nodes (i.e., influence diagrams) supported?
- Free? 0 = free (although possibly only for academic use). $ = commercial software (although most have free versions which are restricted in various ways, e.g., the model size is limite or models cannot be saved, or there is no API.)
- Undir? What kind of graphs are supported? U = only undirected graphs, D = only directed graphs, UD = both undirected and directed, CG = chain graphs (mixed directed/undirected).
- Inference = which inference algorithm is used? jtree = junction tree, varelim = variable (bucket) elimination, MH = Metropols Hastings, G = Gibbs sampling, IS = importance sampling sampling = some other Monte Carlo method, polytree = Pearl's algorithm restricted to a graph with no cycles, VMP = variational message passing, EP = expectation propagation, SL = the program is designed for structure learning from completely observed data, not state estimation
- Comments. If in "quotes", I am quoting the authors at their request.

If you want your package to be listed, please fill out this form.

Name	Authors	Src	Cts	GUI	Params	Struct	Utility	Free	Undir	Inference	Comments
AgenaRisk	Agena	N	Cx	Y	Y	N	N	$	D	JTree	Simulation by Dynamic discretisatio
Analytica	Lumina	N	G	Y	N	N	Y	$	D	sampling	spread sheet compatible
B-course	U. Helsinki	N	Cd	Y	Y	Y	N	0	D	?	Runs on their server: view results us
Banjo	Hartemink	Java	Cd	N	N	Y	N	0	D	none	structure learning of static or dynam
Bayesia	U. Helsinki	C++	G	N	Y	N	N	0	D	MH	Generates C++ for MCMC. (No long

69 packages!

Open-source tools for PGMs

	Weka	JavaBayes	Elvira	BNT	Riso	UnBBayes	OpenMarkov	BayesLine	PNL	BNJ	OBP
Start	1993	1996	1997	1999	2000	2000	2002	2003	2003	2004	2006
Stopped	—	2001	2010	2007	2004	2014	—	2003	2005	2004	2007
Programming language	Java	Java	Java	Matlab	Java	Java	Java	Java	C++	Java	Python
License	GPL	GPL	?	GPL	GPL	GPL	GPL	LGPL	IOSL	GPL	GPL
Bayesian networks	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes
Influence diagrams	no	no	yes	yes	no	yes	yes	no	no	no	no
Dynamic/Markov models	no	no	no	yes	no	no	yes	no	no	no	no
User manuals	yes	yes	yes	yes	yes	yes	yes	no	no	yes	yes
Developer manuals	yes	no	no	no	no	yes	yes	no	no	no	no
Users list/forum	yes	no	no	yes	yes	yes	yes	yes	no	yes	yes
Developers list/forum	yes	no	yes	yes	yes	yes	yes	yes	no	yes	yes
Source HTML docs	yes	yes	yes	no	yes	yes	yes	yes	no	no	no
Version control	yes	no	yes	no	yes	yes	yes	yes	no	yes	yes
Bug tracker	yes	yes	no	no	yes	yes	yes	yes	no	yes	yes

- Among the tools having a GUI for editing PGMs, only Weka and OpenMarkov are still under active development.
- Only BNT and OpenMarkov can represent Markov models.
- Only OpenMarkov has cost-effectiveness analysis.

Which software tool should I use?

- It depends on:
  - my problem → type of model
  - my expertise: tools I am proficient at
  - my budget
  - the recipient: a company, an agency (e.g., NICE)
- Several types of temporal models
  - Markov models (cohort models or microsimulation)
  - discrete event simulation
  - dynamic models (differential equations)

Comparison of MIDs with other techniques

- MIDs vs. spreadsheets (Excel)
  - no need to write any formulas nor VisualBasic macros
  - no need to multiply the number of states (e.g., tunnel states)
  - difficult to write functions of parameters in OpenMarkov
- MIDs vs. Markov decision trees
  - much more compact $\Rightarrow$ possible to build much larger models
  - no need to add tracking variables (microsimulation)
- MIDs vs. a programming language (R, C++, MATLAB…)
  - no need to write any code, not even for sensitivity analysis
  - but programming languages are much more flexible
- MIDs vs. discrete event simulation
  - cohort propagation (exact algorithm) is often much faster
- MIDs vs. all the others: may contain several decisions.

Our (biased) recommendation

for atemporal and Markov models

- If OpenMarkov satisfies your needs, use it
  - because of graphical user interface
  - because of advanced algorithms (difficult to implement)
- If the model is small and relatively simple, you may try using Excel or TreeAge
- Otherwise, use R
  - DARTH group, https://darthworkgroup.com
    software and other resources for CEA in R
- If you have patient-level data, use R+BUGS
  - http://www.statistica.it/gianluca/tags/bcea
    Book: Baio et al., *Bayesian Cost-Effectiveness Analysis with the R package BCEA*, 2017.

8. Conclusions

Conclusions

- BNs overcame the limitations of the naïve Bayes method.
- IDs have several advantages over decision trees, but also have serious limitations for medical decision making.
- DANs are similar to IDs, but more suitable for asymmetric decision problems, especially partially ordered decisions.
- It is possible to do cost-effectiveness analysis with IDs.
- and also with Markov IDs (MIDs) if all decisions are atemporal.
- There are other types of Markov PGMs having one or more decisions per cycle: MDPs, POMDPs, DLIMIDs…

Thank you very much for your attention!

- Links
  - www.cisiad.uned.es
  - www.OpenMarkov.org
  - www.ProbModelXML.org/networks
- Contact: fjdiez@dia.uned.es