Multi-criteria decision support for evidence-based decision making

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Introduction: a simple example of evidence-based medicine

Q: Should we advise parents to administer over the counter cough medicines for acute cough?

- Aims: To determine the effectiveness of over the counter (OTC) cough medicines for acute cough in children (...)
- Methods: Systematic review of randomised controlled trials (RCTs) (...)

Schroeder & Fahey, BMJ, 2002

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- Aims: To determine the effectiveness of over the counter (OTC) cough medicines for acute cough in children (...)
- Methods: Systematic review of randomised controlled trials (RCTs) (...)
- Results: Six trials involving 438 children met all inclusion criteria. Antitussives, antihistamine–decongestant combinations, other fixed drug combinations, and antihistamines were no more effective than placebo in relieving symptoms of acute cough (...) Most drugs appeared to be well tolerated with a low incidence of mostly minor adverse effects.
- Conclusion: **OTC cough medicines do not appear more effective than placebo in relieving symptoms of acute cough** (...)

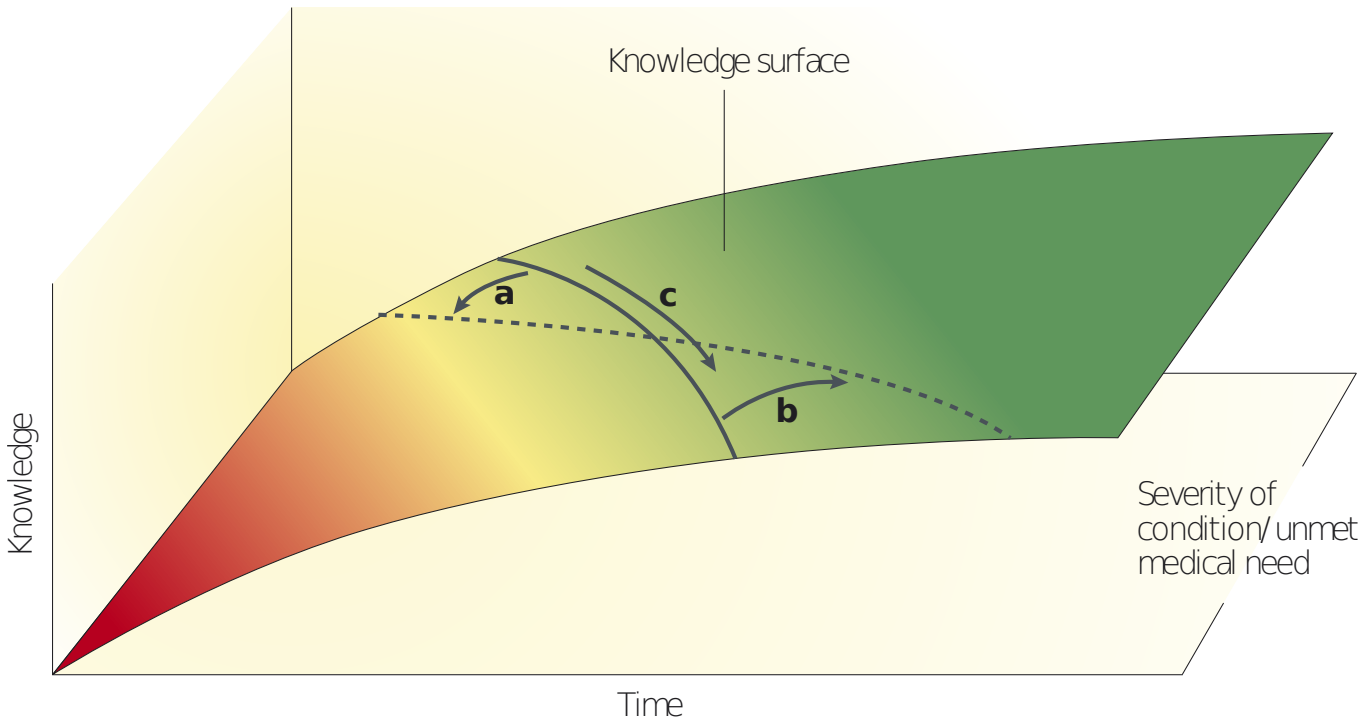
Schroeder & Fahey, BMJ, 2002

Introduction: evidence-based medicine (EBM)

- Evidence-based medicine aims to apply the best available evidence gained from scientific research to medical decision making
- A large share of decisions made by health care professionals are informed by evidence-based medicine, e.g. prescription, regulatory- and reimbursement policy decisions
- Although the scientific evidence is transparent and achieved with methodological rigour, the actual decisions are often unstructured, ad hoc and lack transparency as the treatment benefit-risk valuation is not explicit

Introduction: application of EBM in drug benefit-risk analysis

- For a drug to be granted marketing authorization, it must be proven efficant, safe, and have a sufficient benefit-risk (BR) profile compared to other drugs already in the market



Eichler & al., Nature Drug Disc, 2008

Project Escher

- Escher is a national research project of the Dutch Top Institute Pharma that aims to improve drug regulation through science
- 16 PhD students and 4 PostDocs working in 5 universities (RUG/UMCG, UU/UMCU, Erasmus MC) in collaboration with the industry (Schering-Plough/Merck, GSK, Amgen, WINap)

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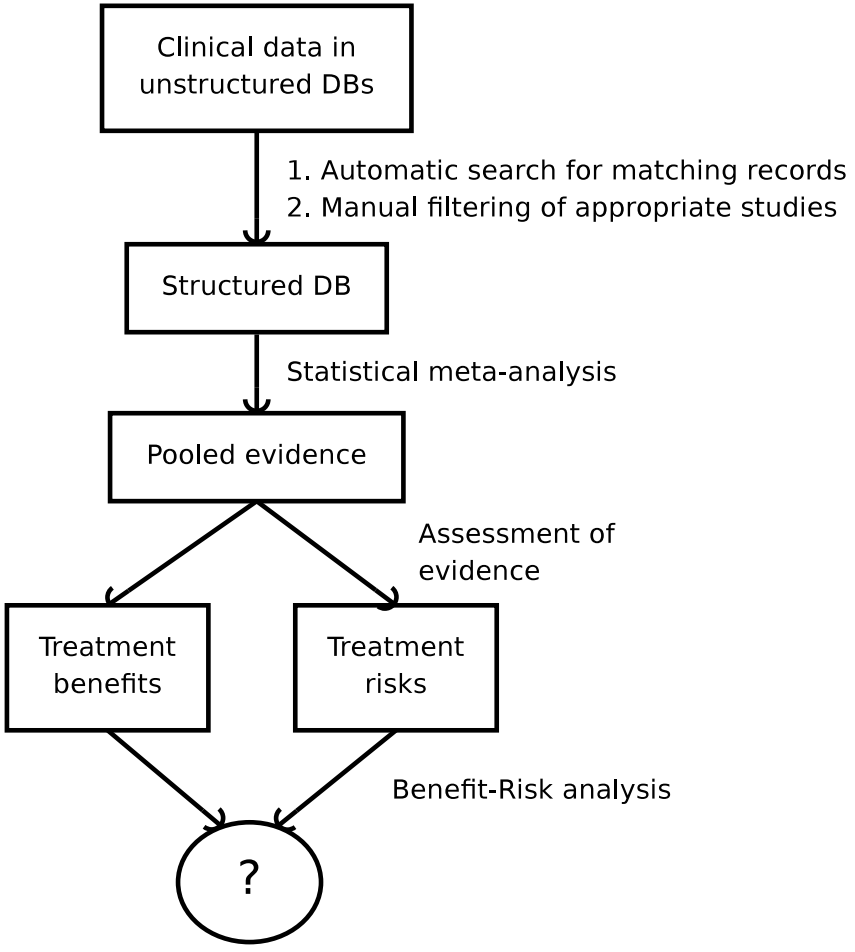
- 16 PhD students and 4 PostDocs working in 5 universities (RUG/UMCG, UU/UMCU, Erasmus MC) in collaboration with the industry (Schering-Plough/Merck, GSK, Amgen, WINap)
- Work package 3.2 (RUG/UMCG with Schering-Plough/Merck) aims to bridge the gap between aggregate clinical data and evidence-based drug regulation by having *useful* methods for benefit-risk analysis implemented in *usable* software (which would then be *used* in real-life decision making)

Useful/Usable/Used: Keen & Sol, IOS Press, 2008

Drug benefit-risk analysis

- BR analysis should include all relevant evidence, and therefore apply (network) meta-analysis



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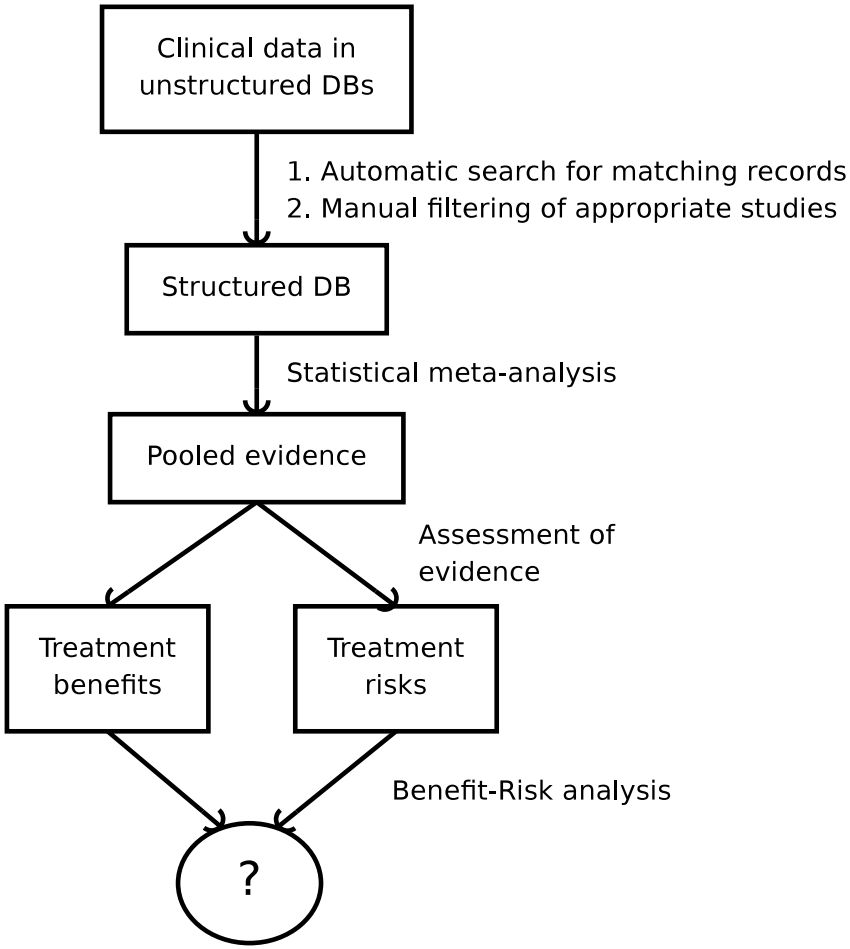
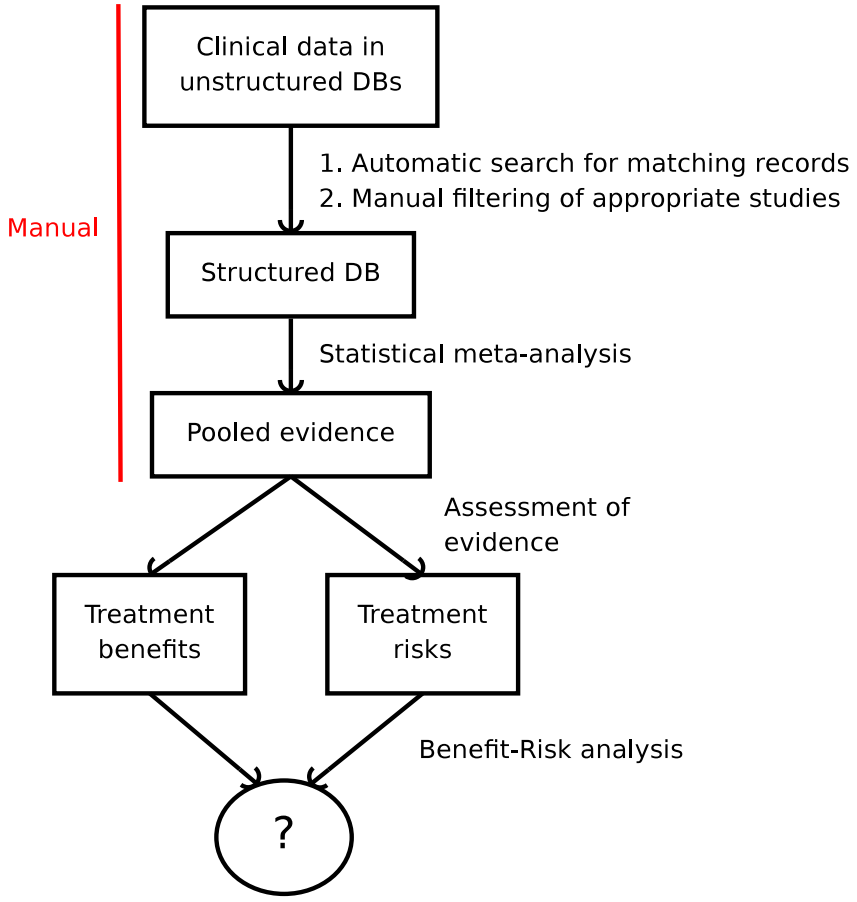


Drug benefit-risk analysis

Problems

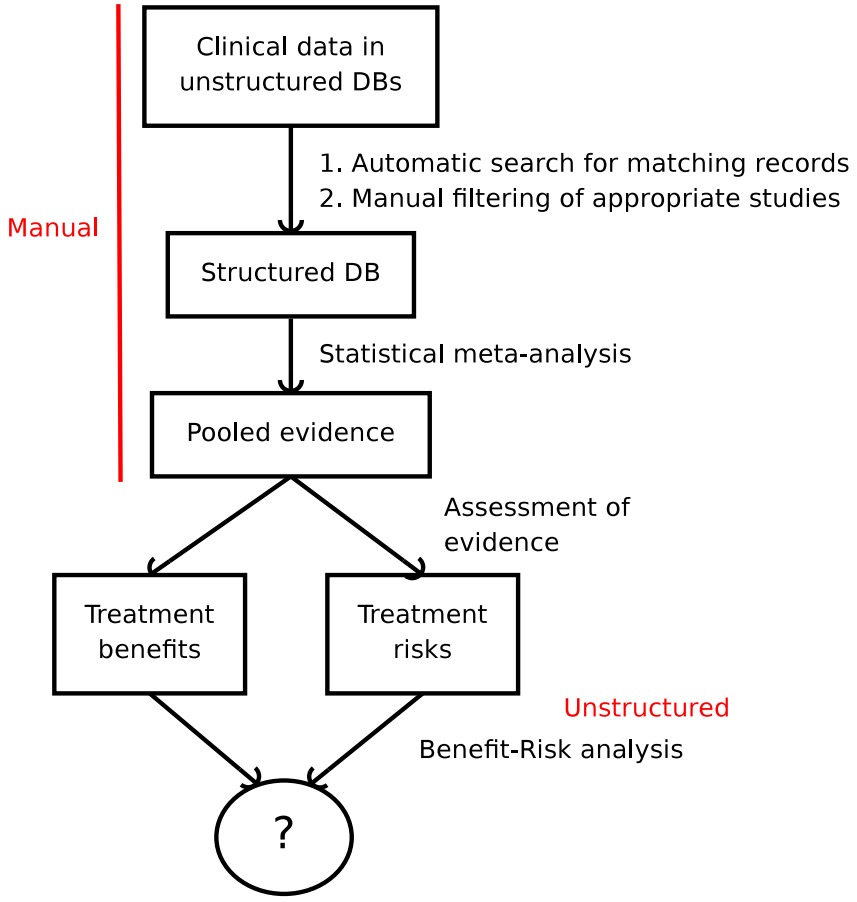
1. Inclusion of all relevant evidence in the meta-analysis is not guaranteed



Drug benefit-risk analysis

Problems

1. Inclusion of all relevant evidence in the meta-analysis is not guaranteed
2. The BR analysis is unstructured and non-transparent



Case study

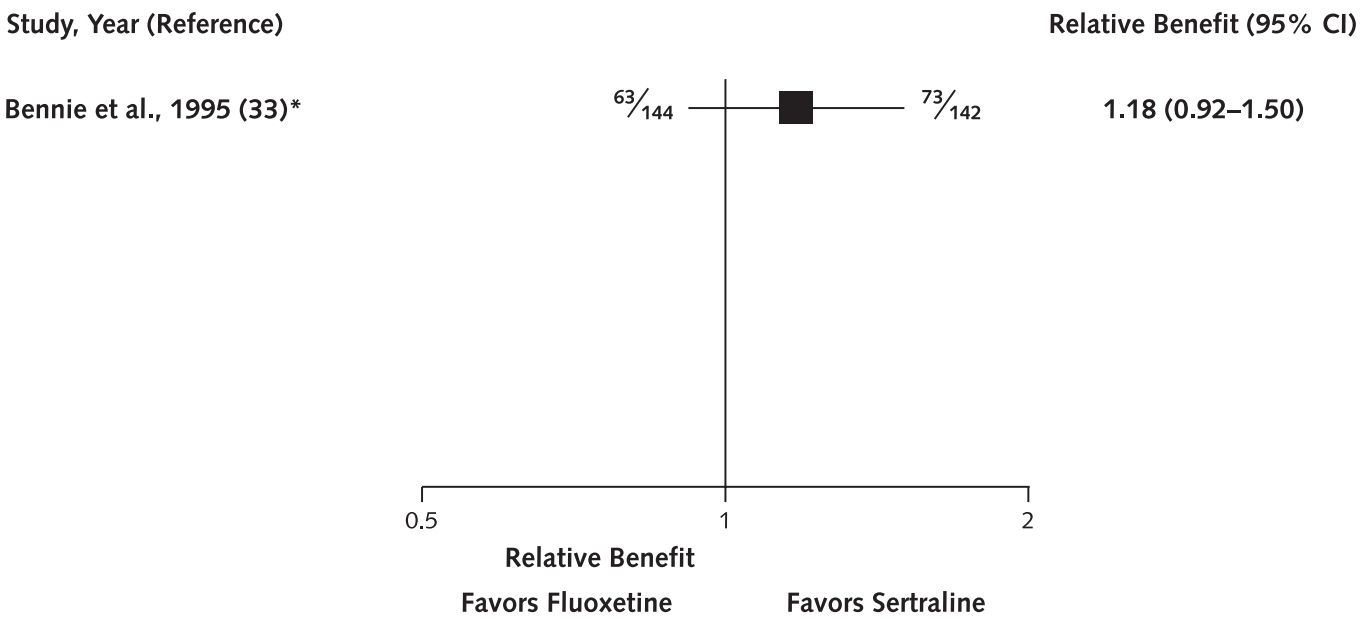
- Hansen & al. (Ann Intern Med, 2005) assessed safety and efficacy of four second generation antidepressants and concluded that there are "no significant differences among the drugs"
- In general, the assessment of antidepressants is hard; placebo effect is always present causing high uncertainty on the results
- Q's:
  1. How can the benefit-risk assessment of second-generation antidepressant be structured based on evidence from the clinical trials?
  2. Can we come up with something better than "no significant differences"?

Case study: data from meta-analysis

Study, Year (Reference)	Fluoxetine	Sertraline
Bennie et al., 1995 (33)*	$^{63}/_{144}$	$^{73}/_{142}$

Hansen & al., Ann Intern Med, 2005

Case study: data from meta-analysis



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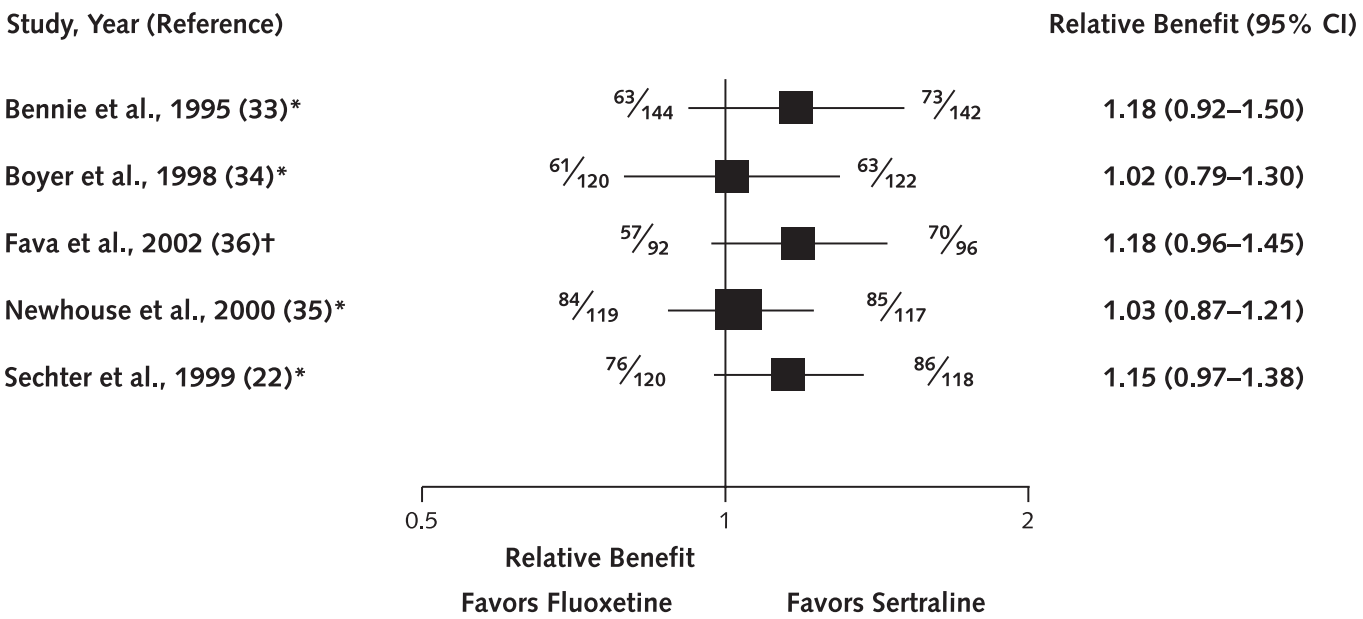

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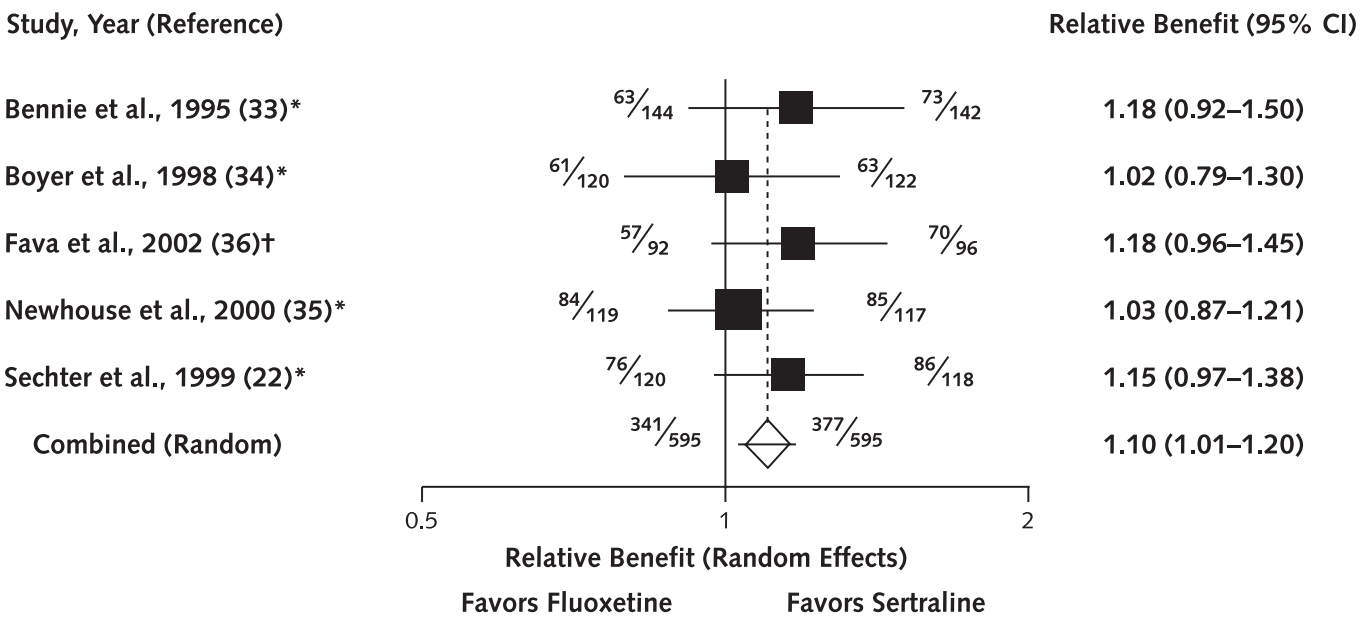

Hansen & al., Ann Intern Med, 2005

Approach

- Separate clinical data (measurements) from the value judgements (MCDA)
- Include all data present in the original analysis (imprecise measurements)
- Provide metrics for decision uncertainty
- Enable model generation for re-applicability

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- Separate clinical data (measurements) from the value judgements (MCDA)
- Include all data present in the original analysis (imprecise measurements)
- Provide metrics for decision uncertainty
- Enable model generation for re-applicability
- We chose to apply Stochastic Multicriteria Acceptability Analysis (SMAA)

SMAA/MAUT notation

- SMAA is a multi-criteria decision aiding (MCDA) method for ranking a set of m alternatives $X = \{x_1, \ldots, x_i, \ldots, x_m\}$ evaluated on basis of a set of n criteria $G = \{g_1, \ldots, g_j, \ldots, g_n\}$
- The evaluation of alternative x_i on criterion g_j is denoted with $g_j(x_i)$
- Preference information expressed with a weight vector w and a value function $u(x_i, w)$ of a commonly accepted shape
- In practice we usually apply an additive linear value function:

$$u(x_i, w) = \sum_{j=1}^{n} g_j(x_i) w_j$$

Lahdelma & Salminen, EJOR, 1998 / Tervonen & Figueira, JMCDA, 2008

SMAA history

- In 1990, Helsinki decided that Vuosaari needed to be reserved for a general cargo harbour. In 1992 a new city plan was approved

- Environmental Impact Assessment (EIA) needed to be done
- EIA required valuations supporting each alternative to be described
- Politically very sensitive decision: DMs are not willing to provide preference information
- $\Rightarrow$ development of SMAA

Hokkanen & al., Socio-Economic Planning Sciences, 1999

Inverse approach

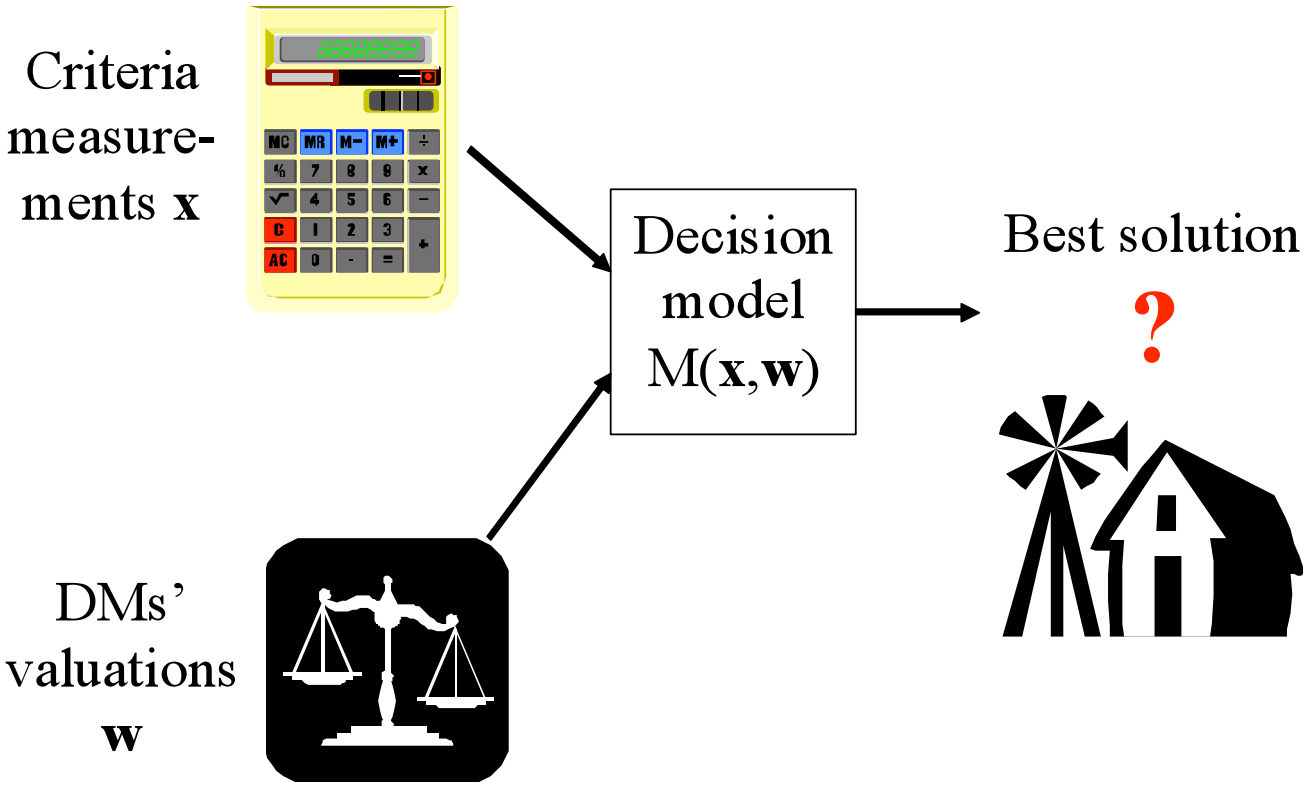


Figure: Traditional MAUT

Lahdelma & Salminen, Springer, 2010

Inverse approach

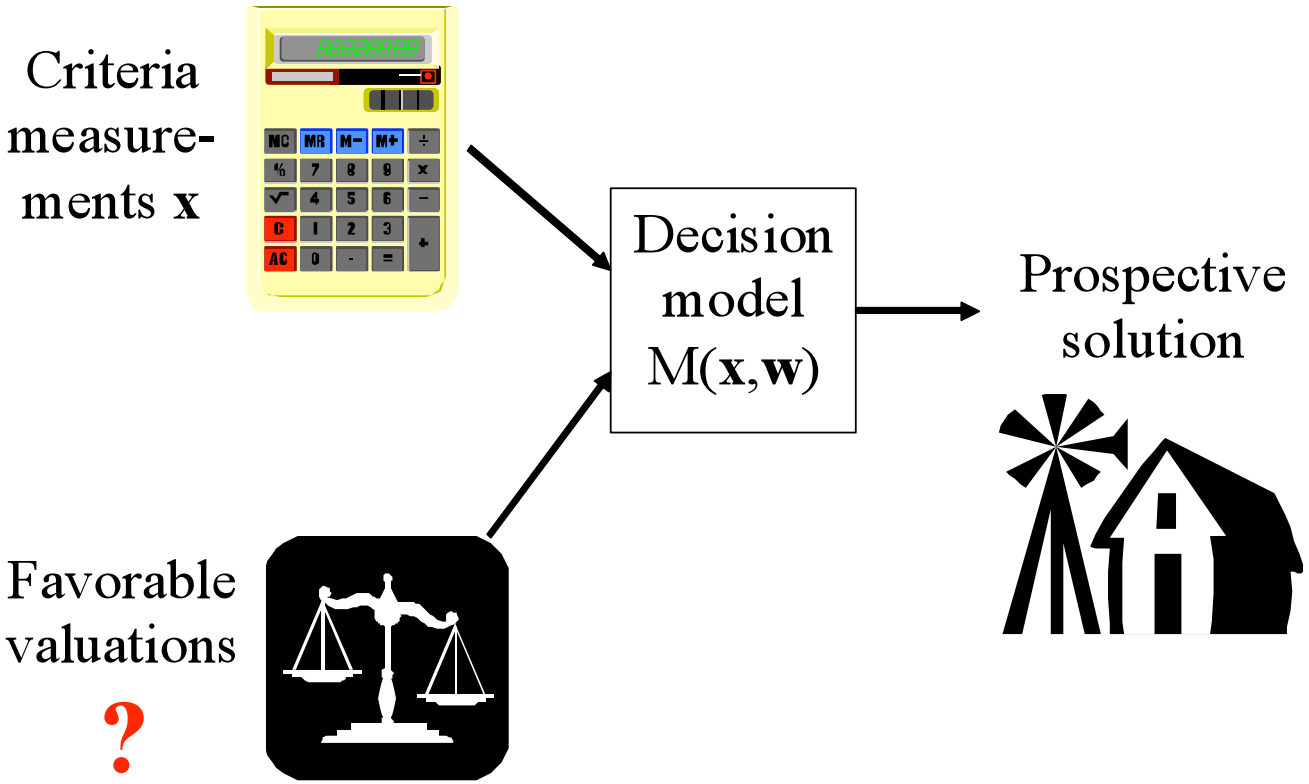
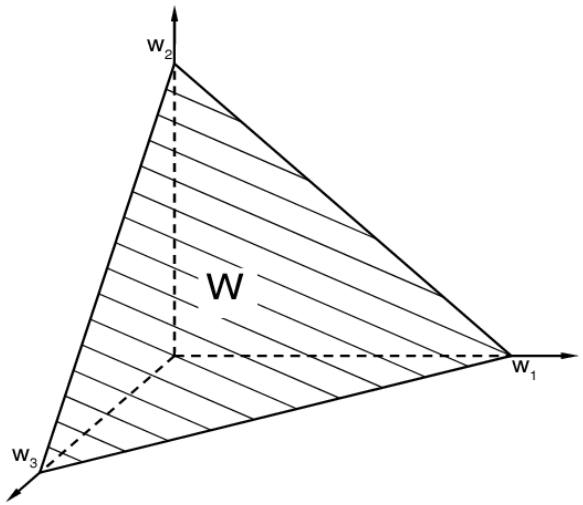


Figure: SMAA

Lahdelma & Salminen, Springer, 2010

Weight space

$$W = \left\{ w \in R^n : w \geq 0 \text{ and } \sum_{j=1}^{n} w_j = 1 \right\}$$



- The joint probability distribution of the weight space is uniform, representing total lack of preference information:

$$f_W(w) = 1/\text{vol}(W)$$

Criteria measurements

- Uncertain or imprecise criteria values are represented by stochastic variables ξ_{ij} with assumed or estimated joint probability function distribution and density function $f_\chi(\xi)$ in the space $\chi \subseteq R^{m \times n}$
- Stochastic variables ξ_{ij} are used to map the deterministic value functions to value distributions $u(\xi_i, w)$
- SMAA is based on analyzing the sets of weights making an alternative the most preferred one:

$$W_i(\xi) = \left\{ w \in W : u(\xi_i, w) \geq u(\xi_k, w) \right.$$
$$\left. \forall k \in \{1, \ldots, m\} \right\}$$

The acceptability index

- Describes the share of different weights and criteria measurements making an alternative the most preferred one

$$a_i = \int_{\xi \in \chi} f_\chi(\xi) \int_{w \in W_i(\xi)} f_W(w)\, dw\, d\xi$$

- Used for classifying alternatives into *stochastically efficient* $a_i >> 0$ and inefficient ones (a_i zero or near-zero)

Central weight vector

- Alternatives expected center of gravity of the favourable weight space

$$w_i^c = \int_{\xi \in \chi} f_\chi(\xi) \int_{w \in W_i(\xi)} f_W(w) w \, dw \, d\xi / a_i$$

- Describes the preferences of a typical DM supporting this alternative with the assumed preference model
- Used for inverse approach: instead of asking preferences and giving results, answers the question "which preferences support an alternative to be the most preferred one?"

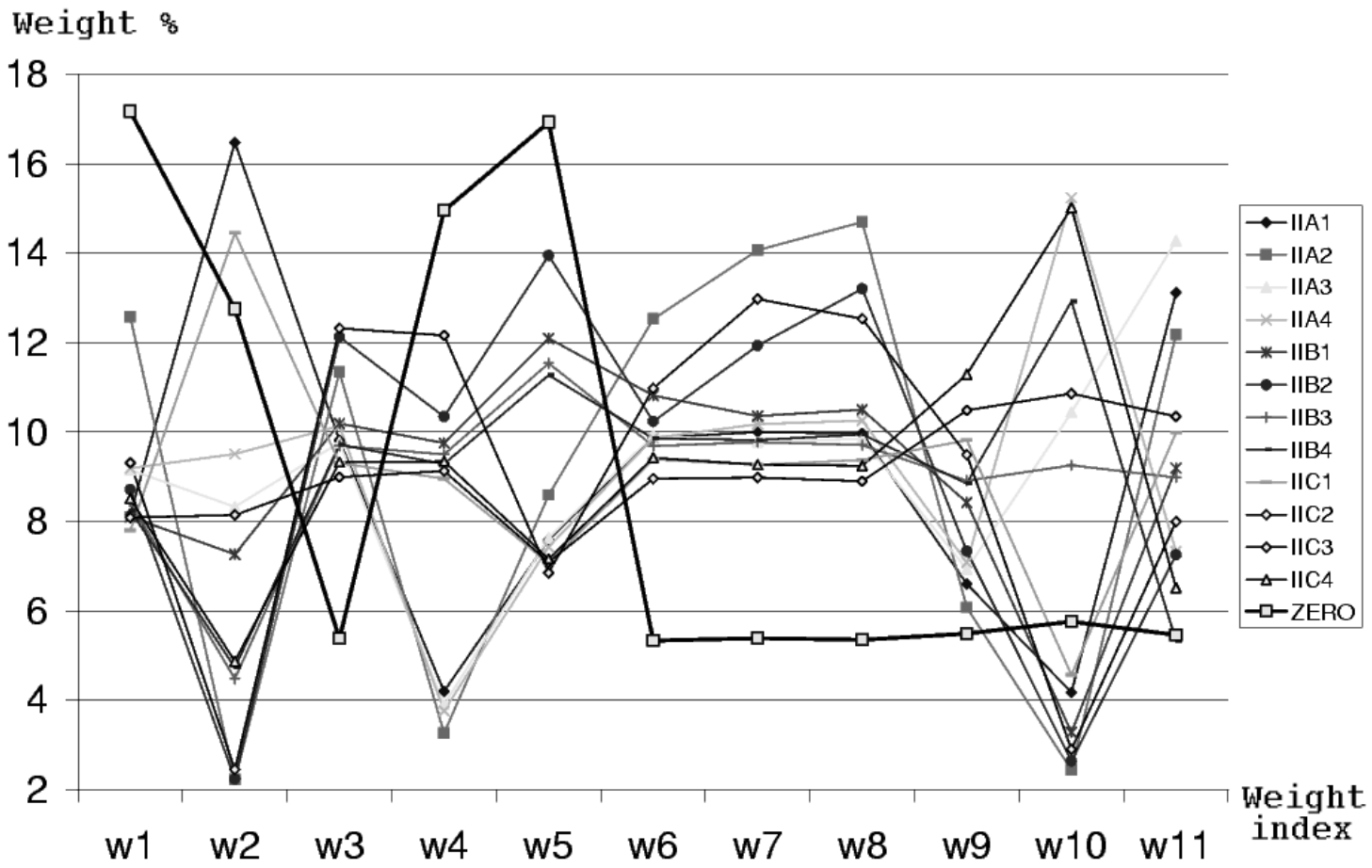


Figure: Central weights of the Vuosaari case

Hokkanen & al., Socio-Economic Planning Sciences, 1999

Confidence factor

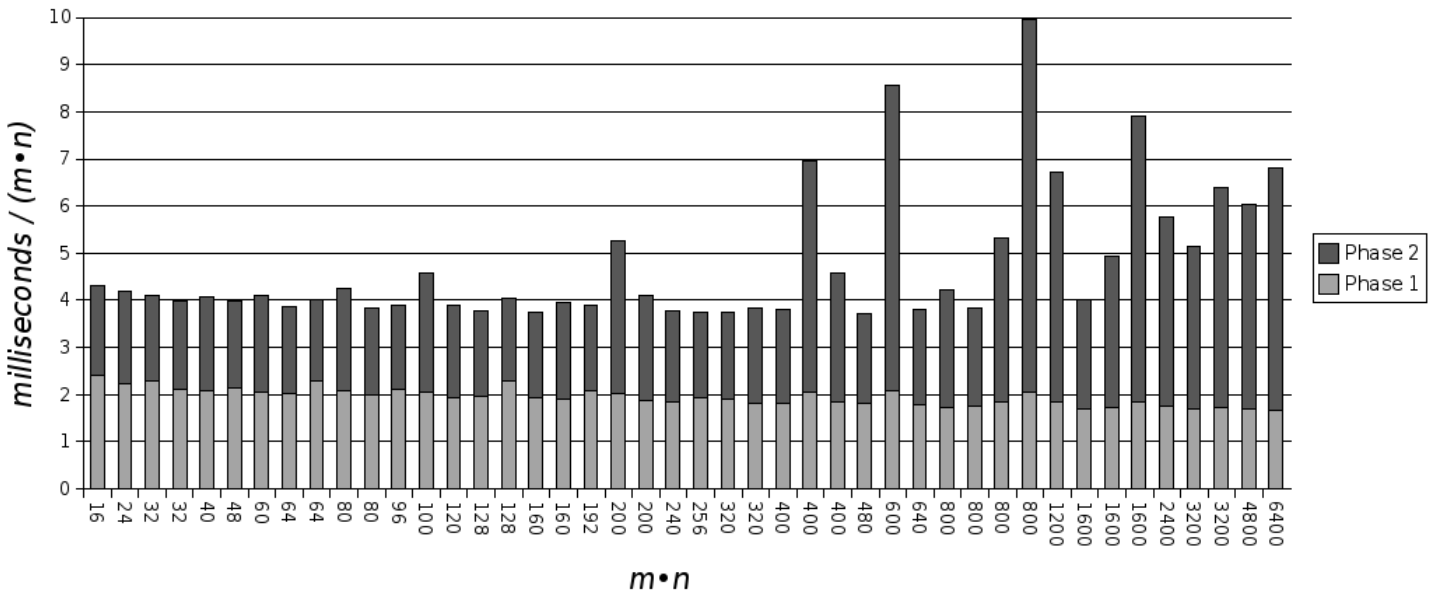
- Probability for an alternative to be the preferred one with the preferences expressed by its central weight vector

$$p_i^c = \int_{\xi \in \chi : u(\xi_i, w_i^c) \geq u(\xi_k, w_i^c)} f_\chi(\xi)\, d\xi$$

- Measures whether the criteria measurements are accurate enough to discern the efficient alternatives
- Used for deciding whether more accurate data should be collected - if low-quality data is enough, savings can be obtained

Computation

- Analytical techniques based on discretizing the integrals with respect to each dimension are infeasible, so the integrals are estimated through Monte Carlo simulation
- 10000 simulations provide sufficient accuracy for the indices
- Algorithm has less-than squared mean complexity and is very fast in practice



Tervonen & Lahdelma, EJOR, 2007

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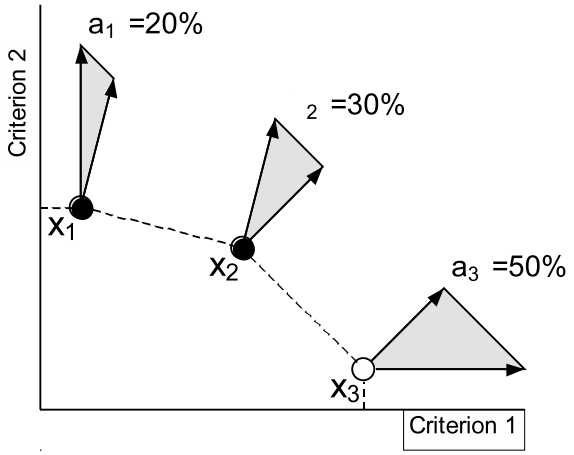
Why did the original SMAA need to be extended?



- Extreme alternatives may obtain excessively high acceptability

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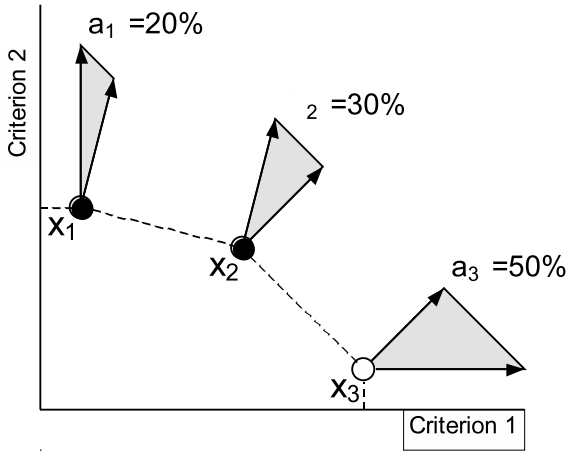

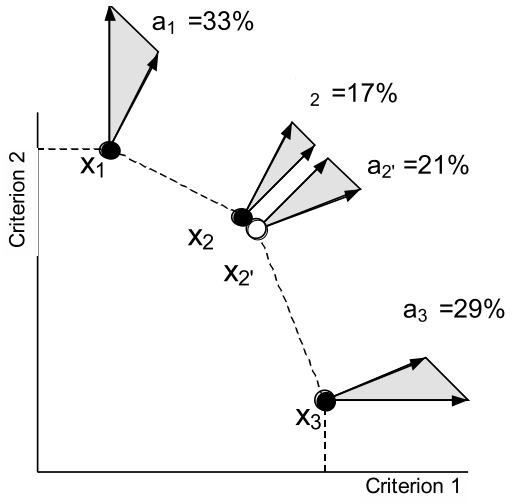

- Extreme alternatives may obtain excessively high acceptability
- Neighboring alternatives decrease each others acceptability

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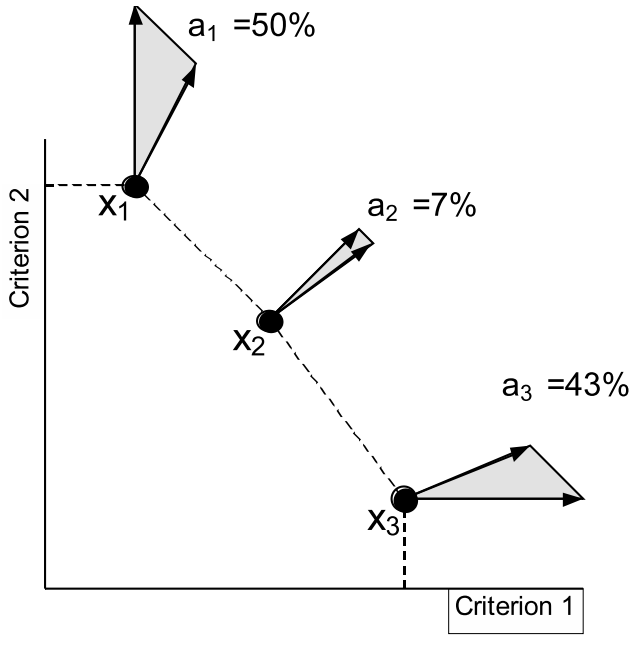

- Good compromise alternatives may obtain too small an acceptability

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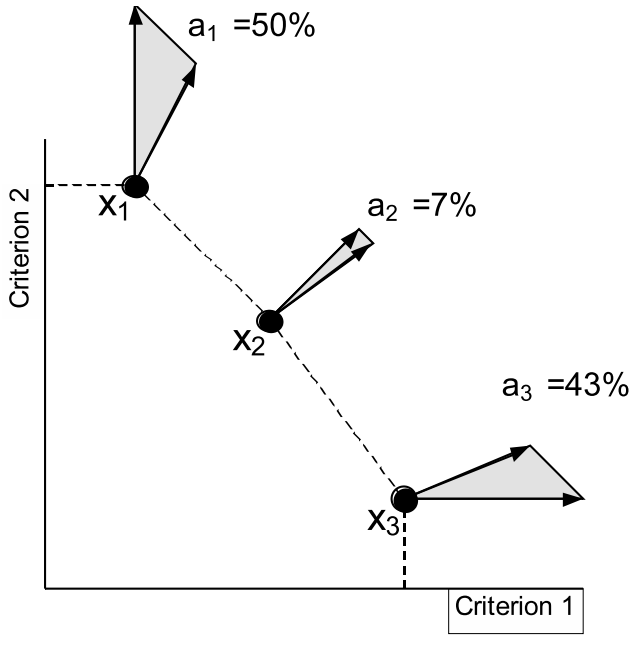


- Good compromise alternatives may obtain too small an acceptability
- No preference information could be taken into account

Modifications in SMAA-2

- The ranking of each alternative is defined as an integer from the best rank ($= 1$) to the worst rank ($= m$) by means of a ranking function,

$$\text{rank}(i, \xi_i, w) = 1 + \sum_k \rho(u(\xi_k, w) > u(\xi_i, w)),$$

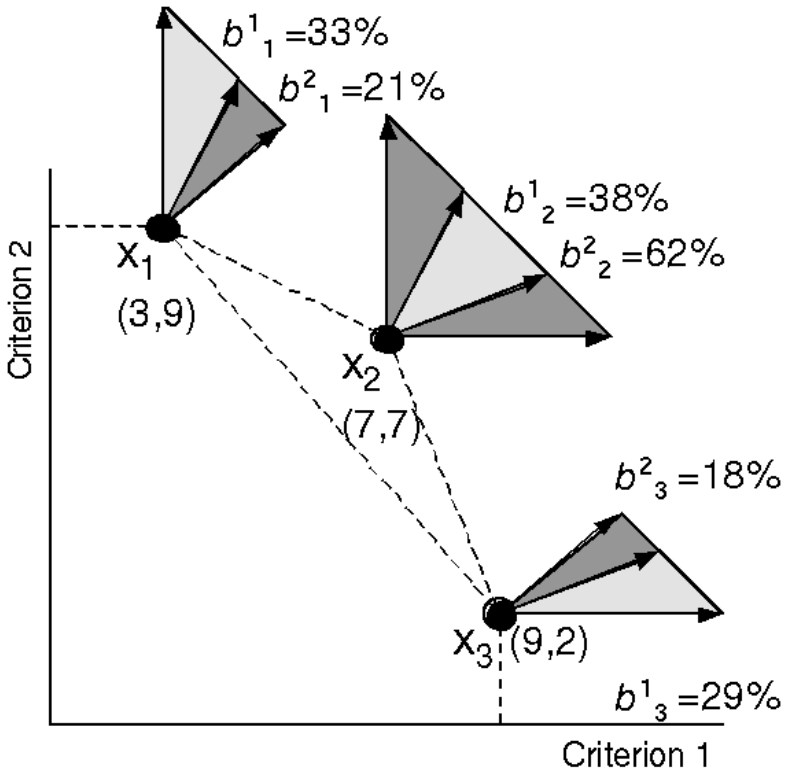
where $\rho(\text{true}) = 1$ and $\rho(\text{false}) = 0$

- The SMAA-2 method is based on analysing the sets of favourable rank weights:

$$W_i^r(\xi) = \{w \in W : rank(i, \xi, w) = r\}$$

Lahdelma & Salminen, Oper Res, 2001

Rank acceptability index



$$b_i^r = \int_{\xi \in \chi} f_\chi(\xi) \int_{w \in W_i^r(\xi)} f_W(w)\, dw\, d\xi$$

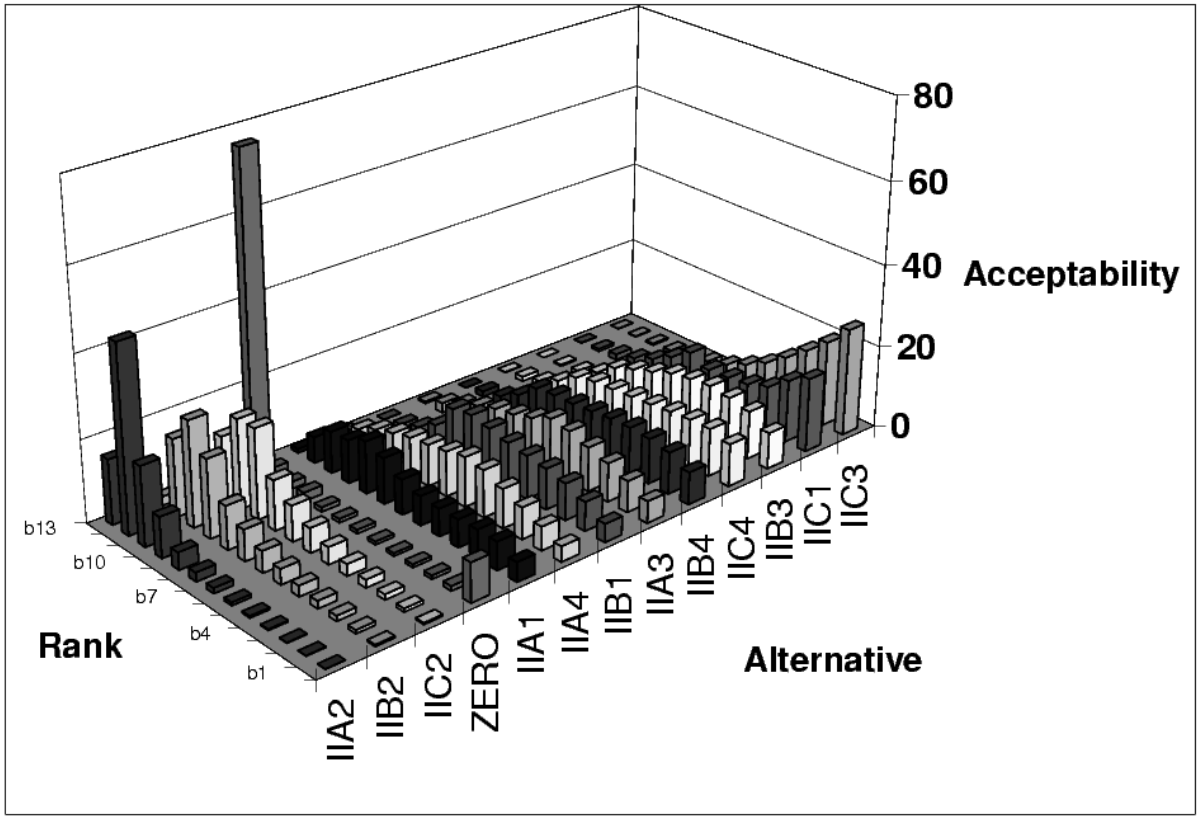


Figure: Rank acceptability indices of the Vuosaari case (Re-analysis)

Lahdelma & Salminen, Oper Res, 2001

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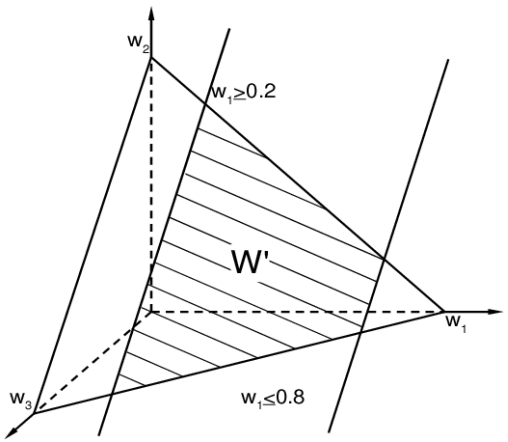
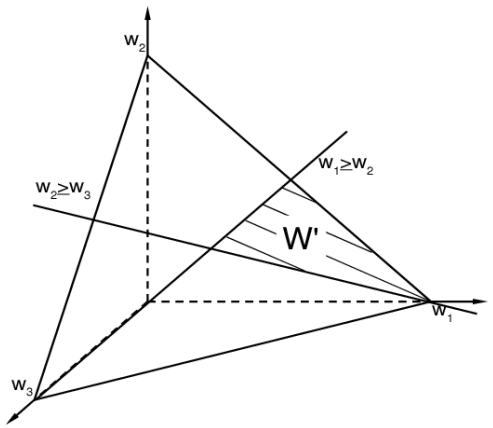
Preference information

- SMAA-2 allows preference information in the form of arbitrary density function in the weight space
- In practice, the weight space is constrained and the density function defined with uniform distribution in the restricted weight space as

$$f'_W(w) = \begin{cases} 1/\mathrm{vol}(W'), & \text{if } w \in W', \\ 0, & \text{if } w \in W \setminus W' \end{cases}$$





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Extensions

- SMAA-O for ordinal criteria that are implemented by simulating all piecewise linear value functions consistent with the ordinal preference information

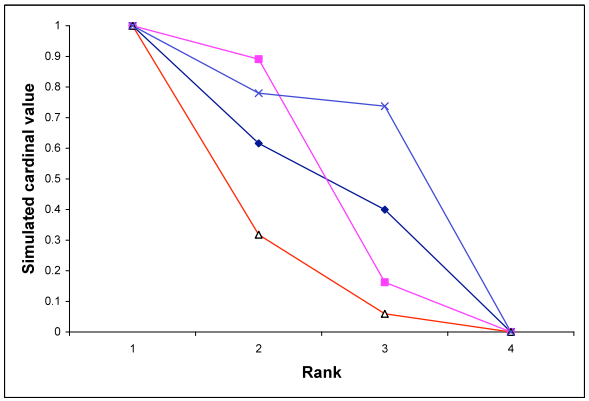

Figure: A sample ordinal-to-cardinal mapping of SMAA-O

- Cross confidence factors for discriminating among very imprecise alternatives
- SMAA-3, SMAA-TRI, SMAA-III, SMAA-D, SMAA-A, SMAA-P, SMAA-CEA, ...

Tervonen & Figueira, JMCDA, 2008

Application: Locating a university kindergarten in Madrid

Figure: Alternative locations

Tervonen & al., Springer, 2010

- San Pablo CEU received a petition from staff in 1996 to build a kindergarten for staff children
- Process was frozen as no agreement over a site could be reached
- In 2007, the process was re-initiated as a two-phase decision process for site selection

Decision problem

- The study included a preliminary phase in which PROMETHEE and generalized criteria were used
- In first phase, alternatives from the 10 year old analysis were used together with old measurements, and the results of this analysis led to a decision to re-initiate the planning process
- Second phase consisted of re-evaluating the alternative sites with up-to-date information

Criteria measurements

Alt	Accessibility min	Size max	Build cost min	Eff/LS rank	Main cost min
C Montepríncipe	52.5 ± 5.24	234	3937880	3.	39000–48000
C Moncloa	39.17 ± 5.85	159	4729000	7.	26000–32000
C Argüelles	36.67 ± 6.06	167	5238520	5.	28500–35000
San Dominique	38.33 ± 6.06	134	4068450	6.	23500–29000
Majadahonda	46.33 ± 3.83	159	3146000	4.	27500–33500
Pozuelo	42.83 ± 3.19	167	3317270	1.	28500–35000
Las Rozas	49 ± 3.52	201	3904800	2.	34000–42000

Preference information

Alt	Acces min	Size max	Build cost min	Eff/LS rank	MT cost min
Weight	0.25–0.35	0.15–0.25	0.25–0.35	0.05–0.15	0.05–0.15
Indif TH	6.5 ± 1.5	1.5 ± 1.5	10000 ± 5000	-	$3\% \pm 2\%$
Pref TH	12.5 ± 2.5	3 ± 1	100000 ± 50000	-	$8\% \pm 2\%$

- The decision makers could provide weights but were uncertain about the exact numerical values, therefore we applied imprecise weights that maintain the criteria ranking

Results - rank acceptability indices (%) of SMAA-III analysis

Alt	1	2	3	4	5	6	7
Montepríncipe	13	19	19	19	17	10	2
Moncloa	9	15	17	16	17	17	10
Argüelles	**36**	16	14	12	12	7	2
S. Dominique	3	10	16	**22**	**22**	19	8
Majadahonda	4	9	14	19	**22**	**20**	12
Pozuelo	**37**	**23**	16	11	7	4	1
Las Rozas	18	**25**	**20**	17	12	7	1

- Pozuelo and Campus Argüelles the "best" alternatives
- Management opted for Pozuelo as acquiring land in Central Madrid is uncertain

Application: Elevator planning

- Modern high-rise building planning includes configuring elevator groups
- In this study, we simulated a 20-floor building
- There are "standard" criteria to use in planning
- Criteria divided into two subgroups:
  - non-performance (cost, floor area)
  - performance (avg waiting/journey time, percentage of waiting/journey times exceeding a threshold)
- Performance criteria depend on the type of building
  $\longrightarrow$ simulation required

Tervonen & al., Omega, 2008

KONE Building Traffic Simulator

- Simulator used by KONE (one of the worlds leading elevator manufacturers) in elevator planning
- Consists of two parts: elevator model and traffic generation

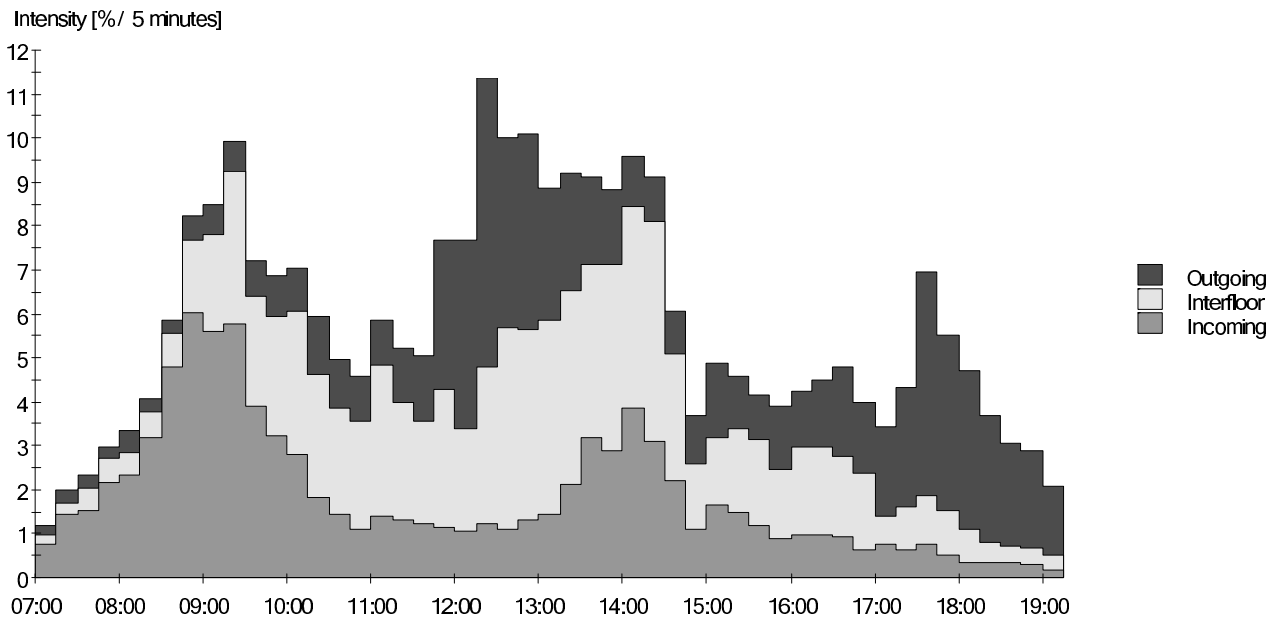

Figure: Traffic profile of the simulated building

Alternatives

- 10 alternative configurations. The number of elevators varies between 6 and 8, rated load from 13 to 24, and speed from 3.5m/s to 5m/s

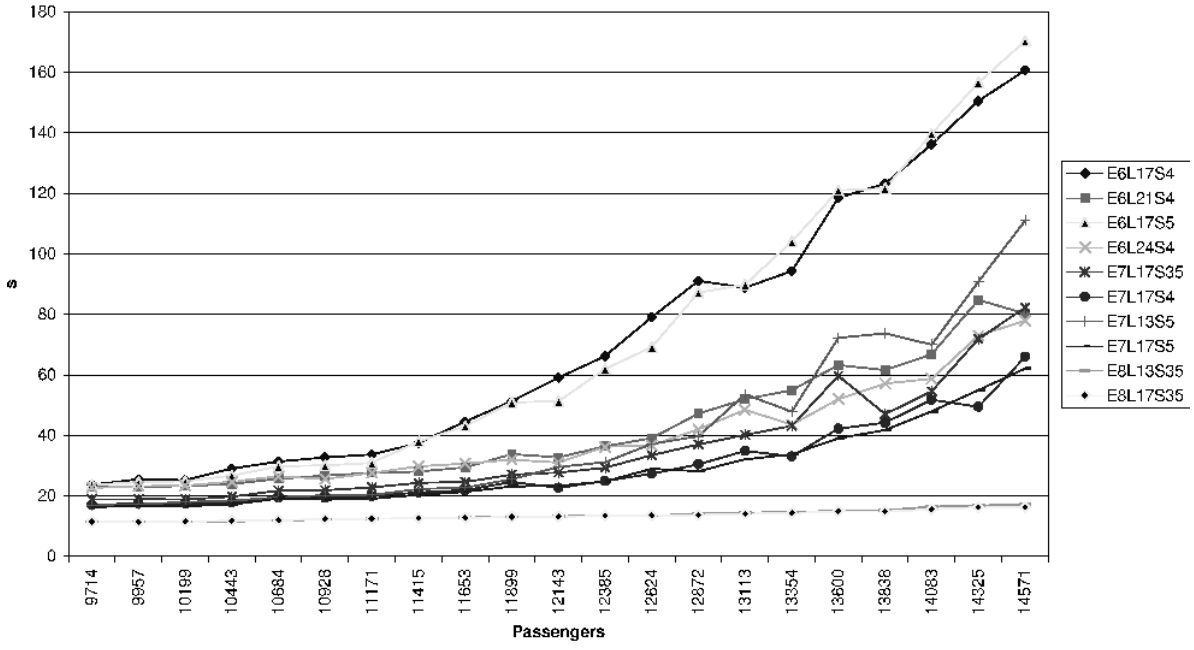

Figure: Average waiting times of the alternatives, obtained from simulation

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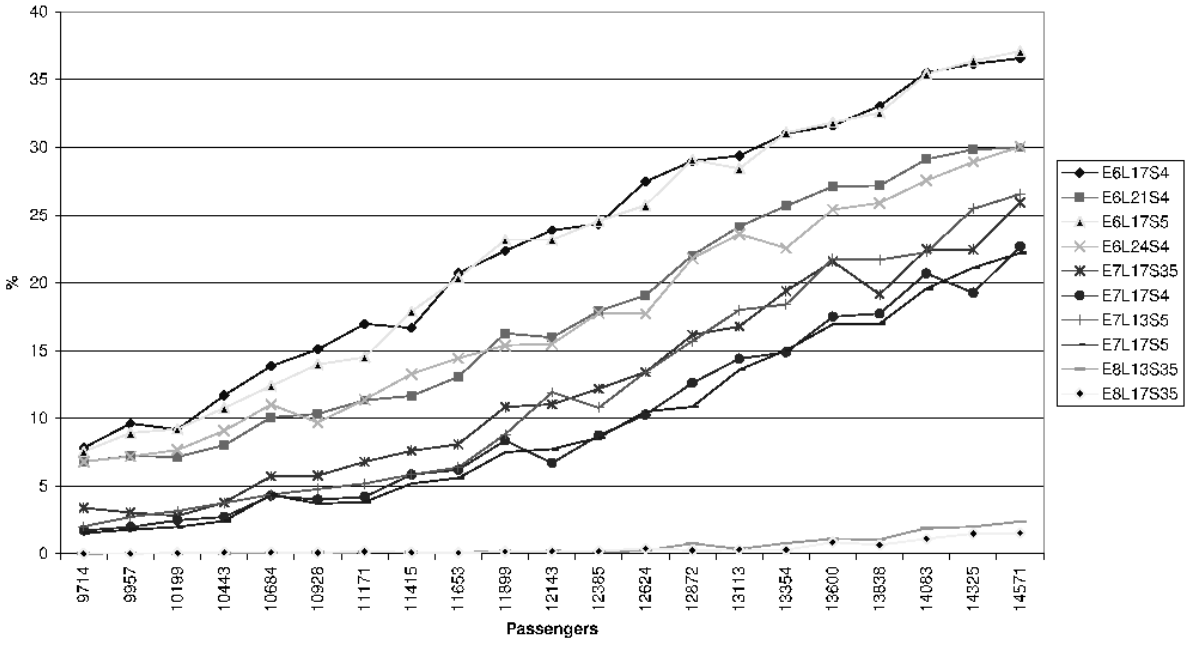

Figure: Percentage of waiting times exceeding 60s, obtained from simulation

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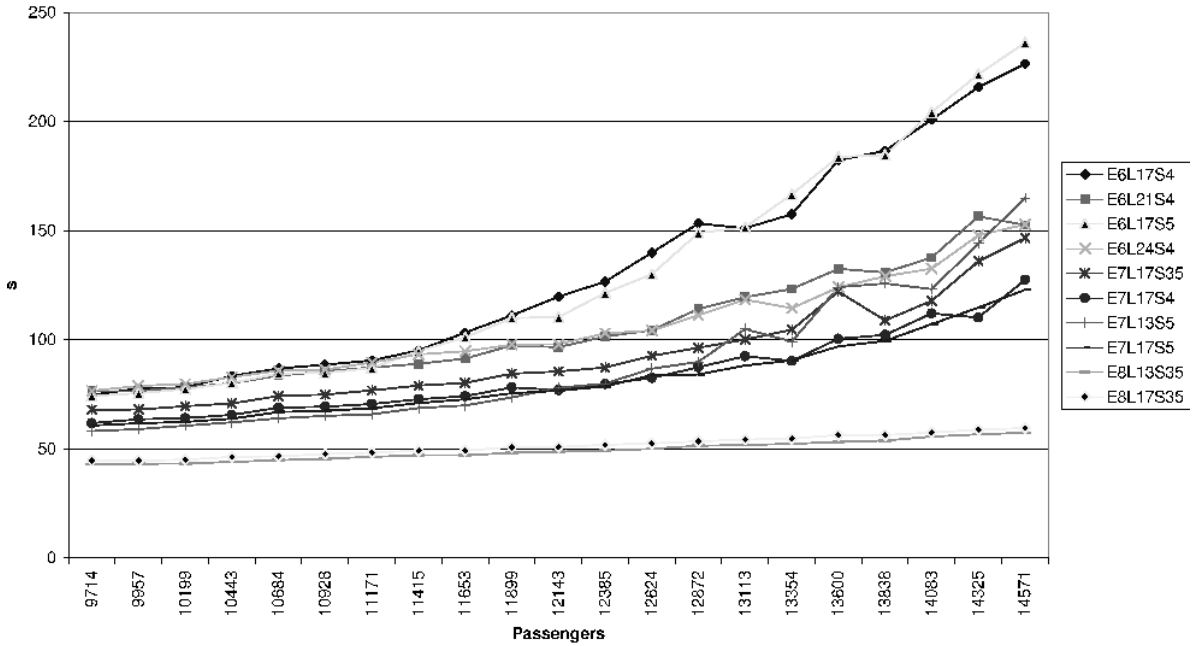

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Alternatives

- 10 alternative configurations. The number of elevators varies between 6 and 8, rated load from 13 to 24, and speed from 3.5m/s to 5m/s

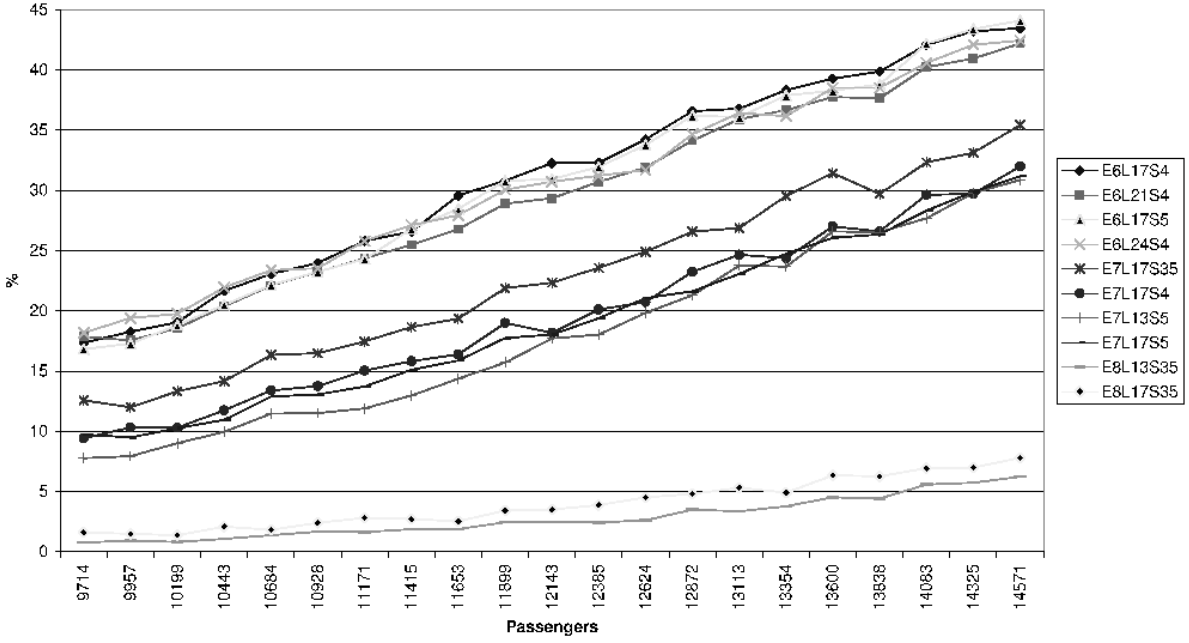
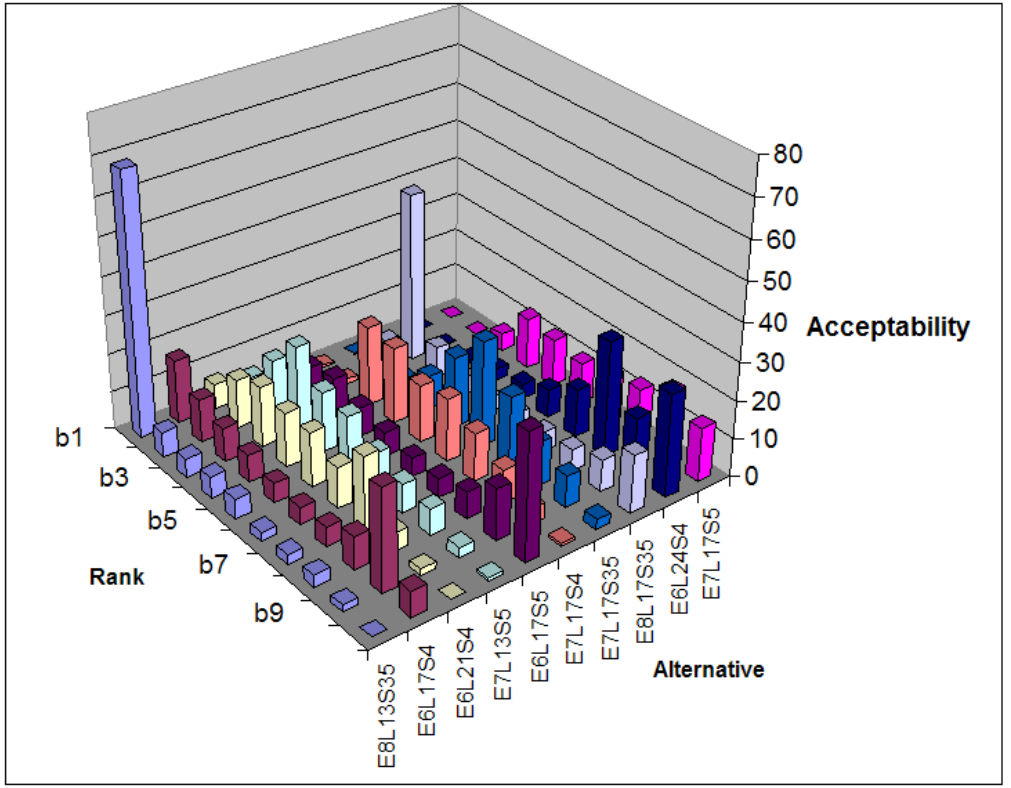


Figure: Percentage of journey times exceeding 120s, obtained from simulation

The model & results

- Very slow elevator simulator & dependent criteria $\longrightarrow$ model the performance criteria as MV Gaussian
- Weight intervals were used to help to balance between performance and non-performance criteria



Tervonen & al., Omega, 2008

Back to BR case study

Problem formulation in SMAA terms:

- m alternative treatments are evaluated with respect to efficacy and $n-1$ most important adverse drug reactions (ADRs)
- criteria measurements for efficacy are lod-odds ratios (normal distributed) compared against Fluoxetine:

Treatment	Mean	95% CI
Fluoxetine	1.00	(1.00 - 1.00)
Paroxetine	1.09	(0.97 - 1.21)
Sertraline	1.10	(1.01 - 1.20)
Venlafaxine	1.12	(1.02 - 1.23)

- measurements for ADR criteria are normal distributed

Tervonen & al., SOM Res Rep, 2010 (submitted to Stat in Med)

Criteria characteristics

Name	Measurement unit	Preference direction
Efficacy	Relative to Fluoxetine	$\uparrow$
Diarrhea ADRs	Absolute %	$\downarrow$
Dizziness ADRs	Absolute %	$\downarrow$
Headache ADRs	Absolute %	$\downarrow$
Insomnia ADRs	Absolute %	$\downarrow$
Nausea ADRs	Absolute %	$\downarrow$

Criteria measurements (given as mean (95% CI))

Crit	Fluoxetine	Paroxetine	Sertraline	Venlafaxine
Eff	1	1.09 (0.97-1.21)	1.10 (1.01-1.20)	1.12 (1.02-1.23)
Dia	11.7 (6.8-16.6)	9.2 (5.6-12.9)	15.4 (10.2-20.6)	5.5 (1.0-10.1)
Diz	7.2 (4.3-10.0)	10.6 (7.5-13.7)	7.5 (4.6-10.4)	15.7 (7.0-24.4)
Hea	16.6 (10.2-23.0)	21.2 (11.1-31.3)	20.2 (12.8-27.6)	12.8 (8.0-17.6)
Ins	13.7 (10.0-17.4)	14.3 (8.6-20.1)	15.0 (8.7-21.3)	11.2 (3.4-19.0)
Nau	8.6 (15.1-22.1)	18.3 (11.1-25.6)	19.5 (14.4-24.6)	31.0 (27.4-34.0)

Preference information

- We considered 3 scenarios:
  1. Health policy decision making with no preferences
  2. Prescription for mild depression
  3. Prescription for severe depression
- Ordinal swing weighting for prescription decisions

Table: Criteria scales

Criterion	Scale range
Efficacy	[0.98, 1.23]
Diarrhea ADRs	[1, 20.6]
Dizziness ADRs	[4.4, 24.4]
Headache ADRs	[8, 31.3]
Insomnia ADRs	[3.4, 21.3]
Nausea ADRs	[11.1, 34]

Results (1)

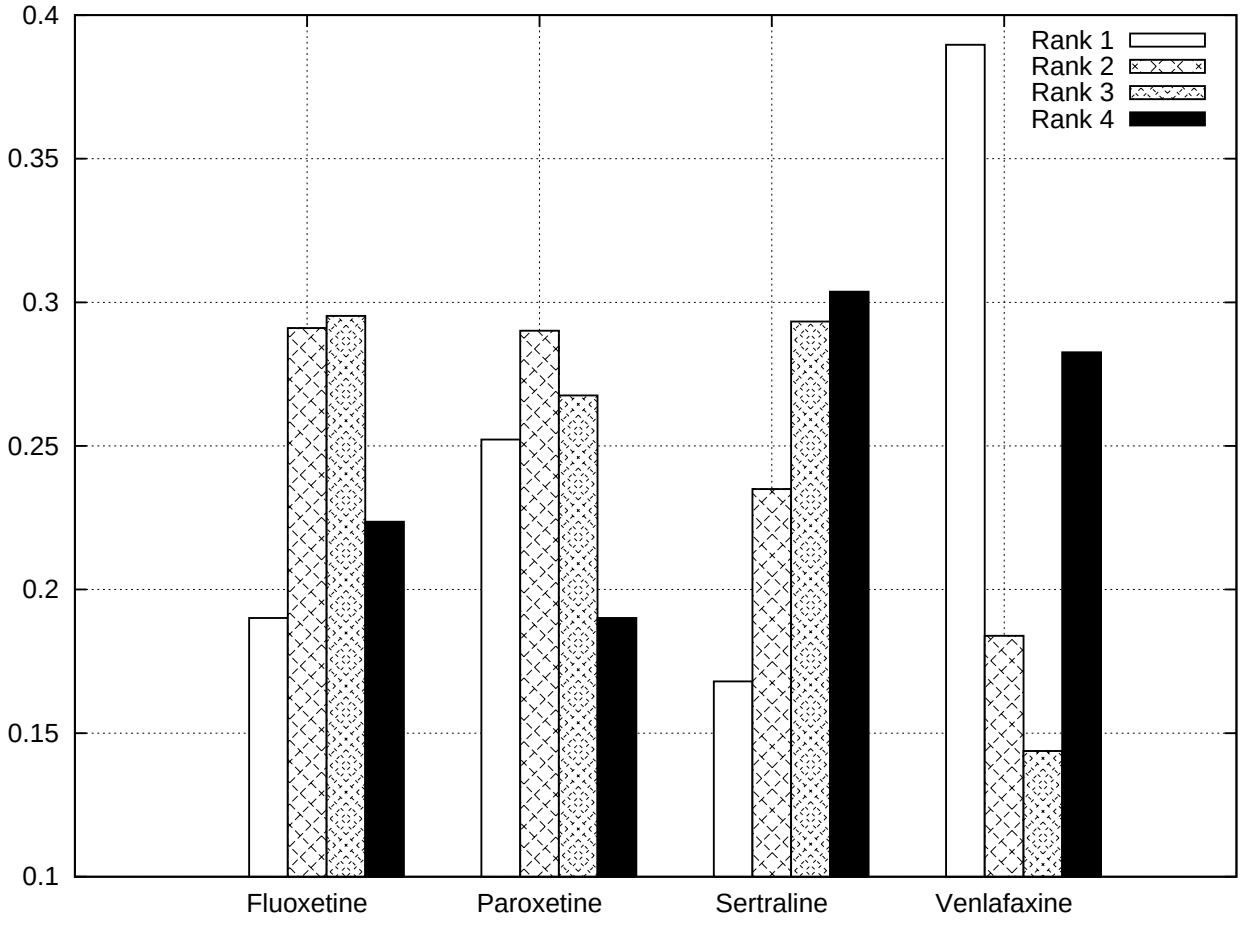


Figure: Rank acceptability indices for the model without preference information.

Results (2)

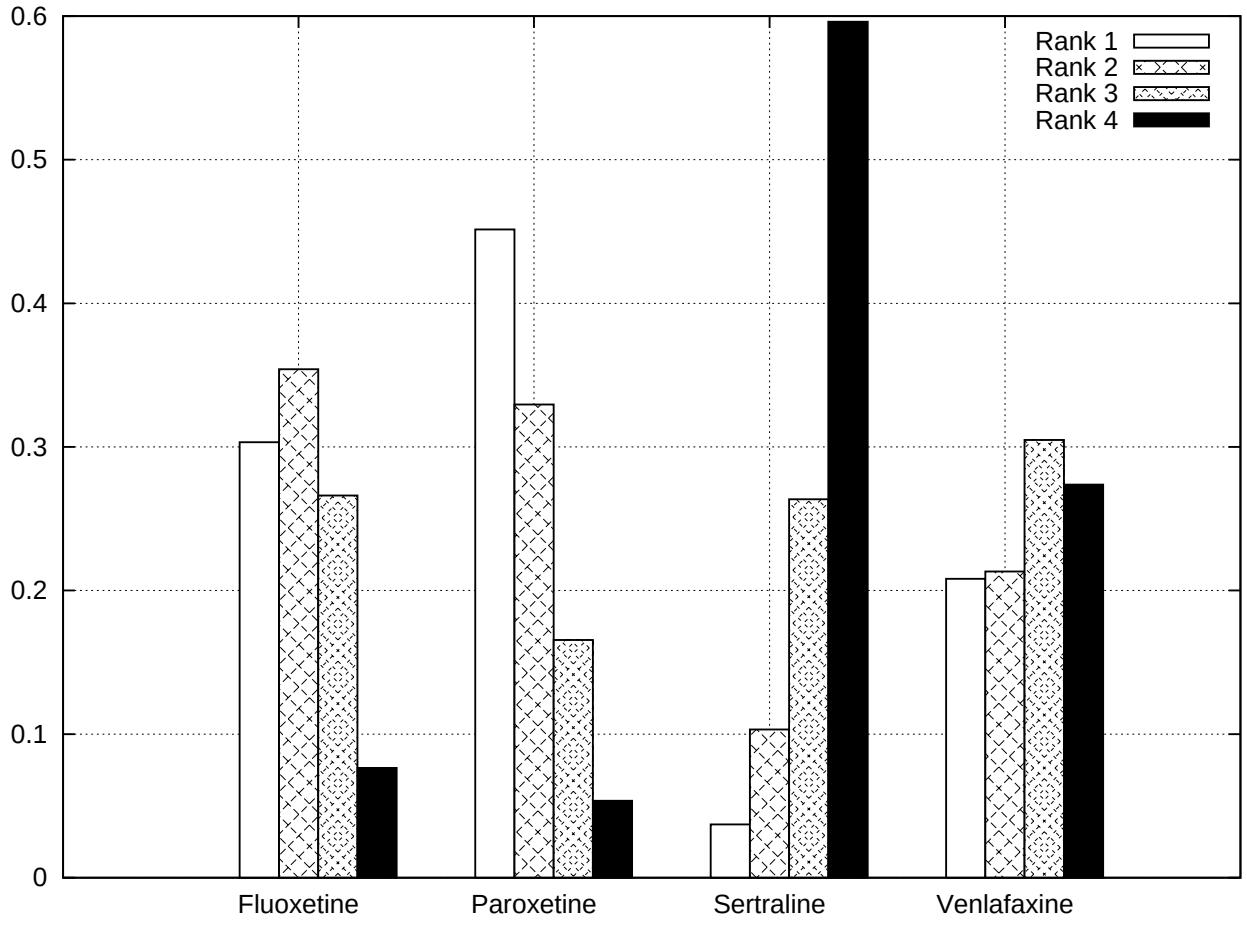


Figure: Rank acceptability indices from the scenario of mild depression.

Results (3)

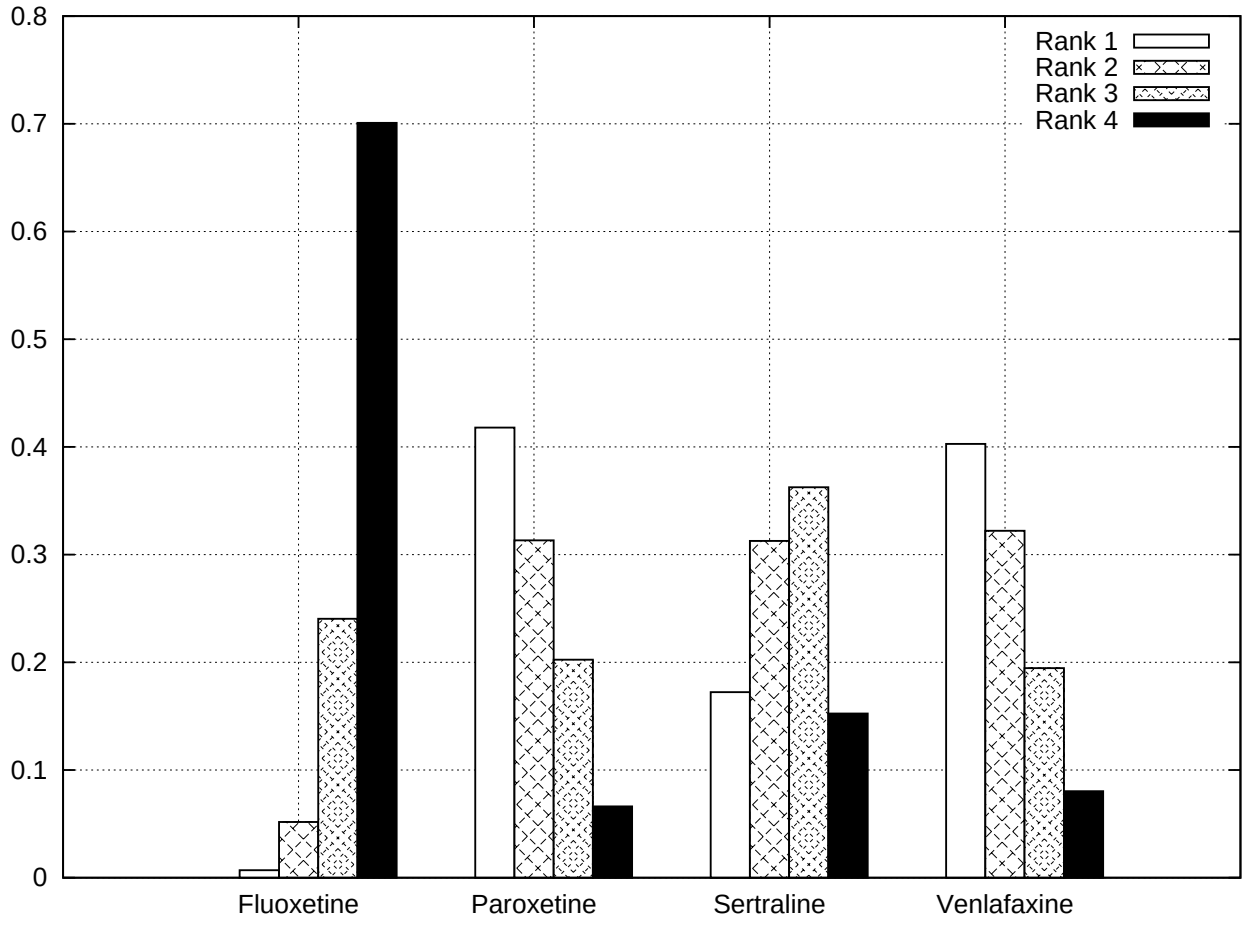


Figure: Rank acceptability indices from the scenario of severe depression.

Was our approach succesful?

- Separate clinical data (measurements) from the value judgements (MCDA)
- Provide metrics for decision uncertainty
- Include all data present in the original analysis (imprecise measurements)
- Enable model generation for re-applicability

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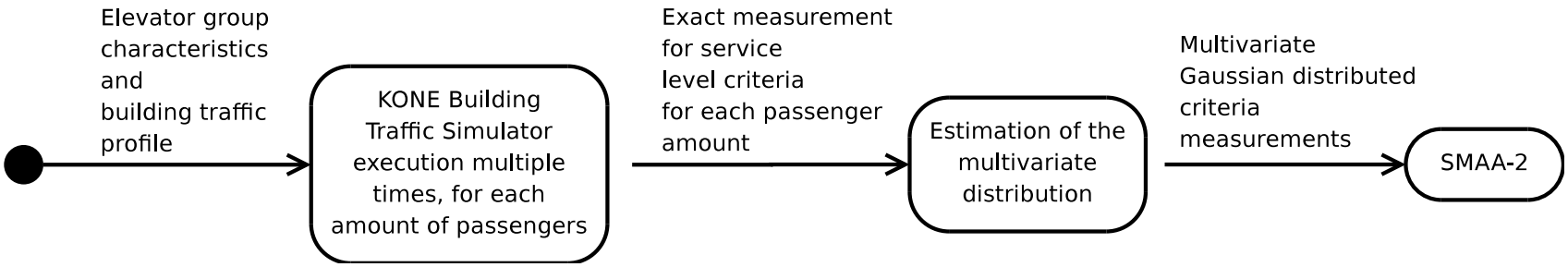
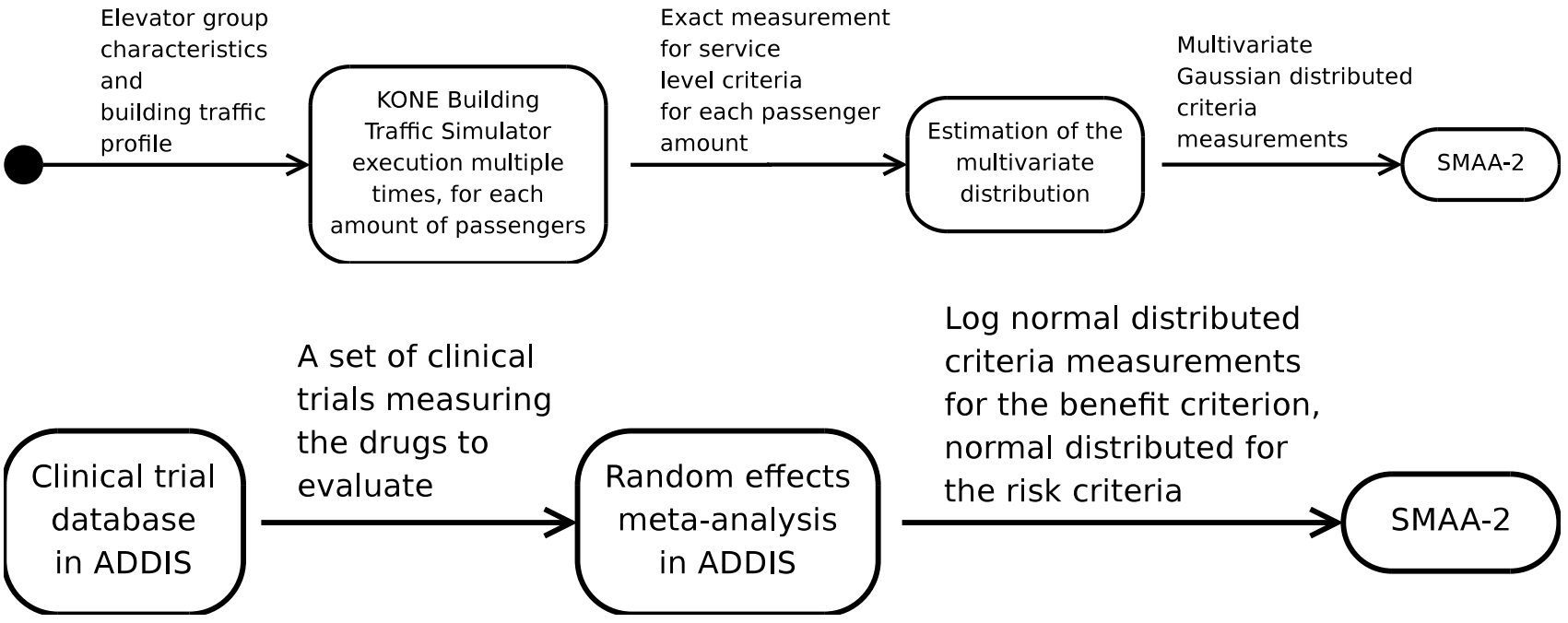
MCDA Model Generation



Tervonen, URPDM'2010

MCDA Model Generation



Tervonen, URPDM'2010

When cannot the MCDA-BR-model be generated?

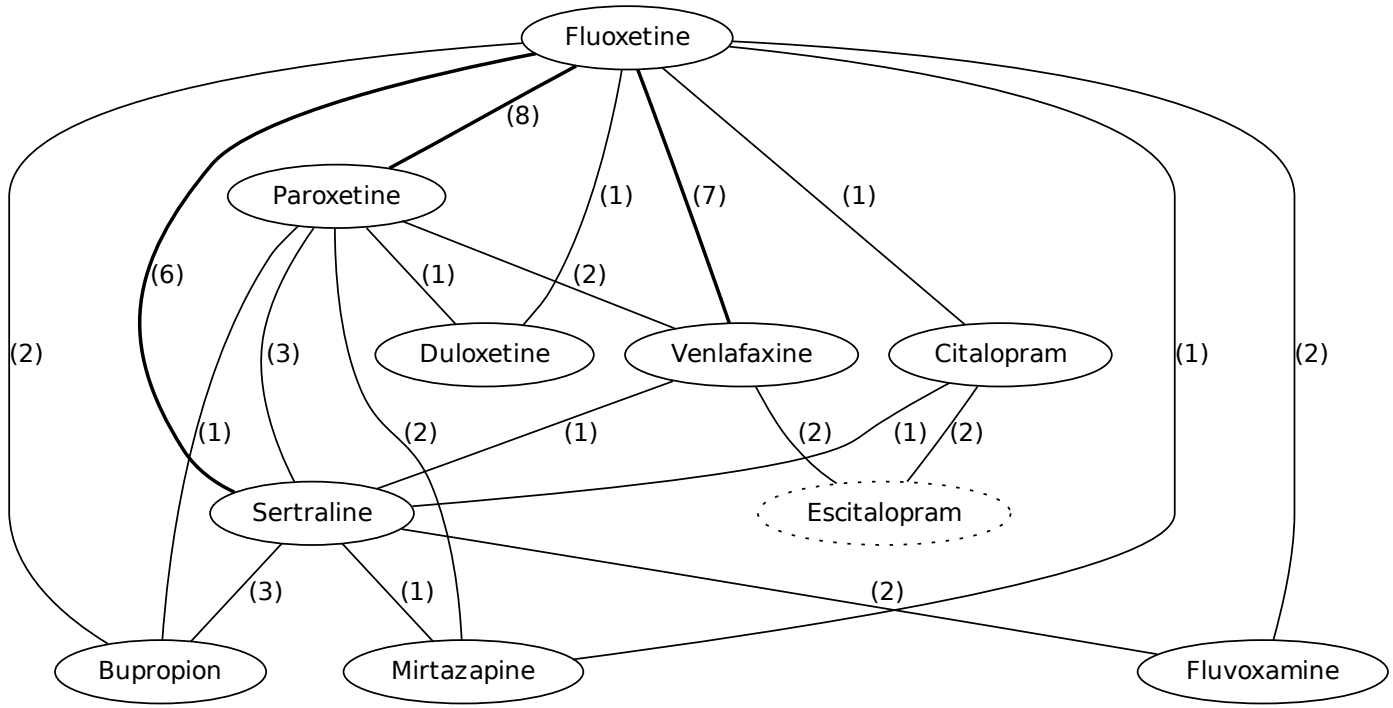


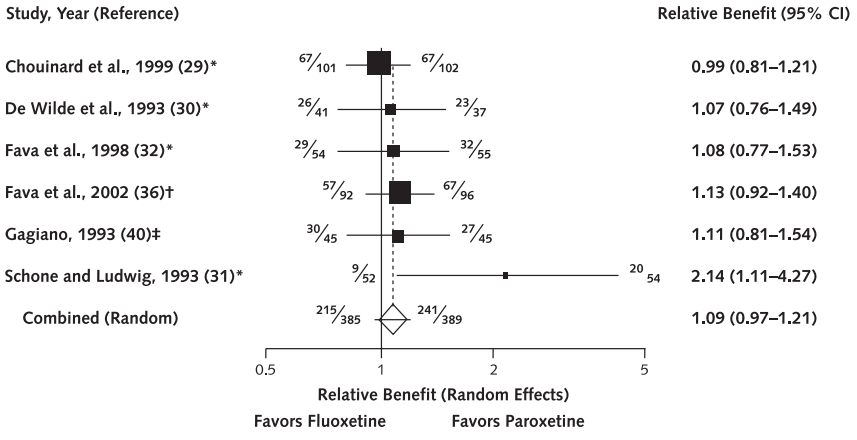
Figure: Evidence network of studies comparing efficacy of 2nd gen antidepressants

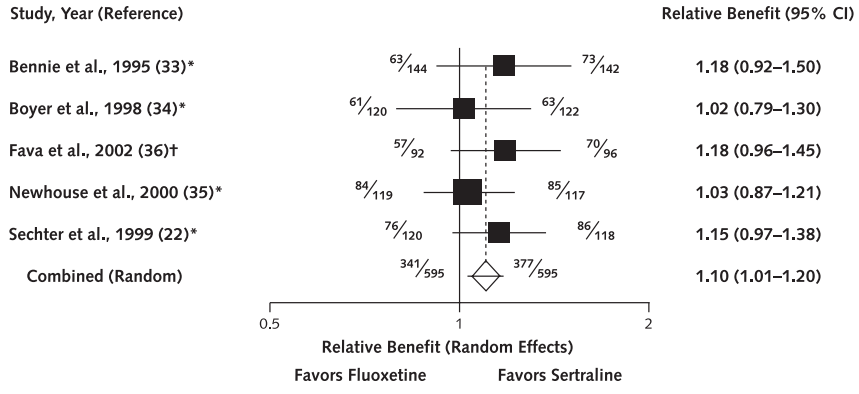
Meta-analysis limitations

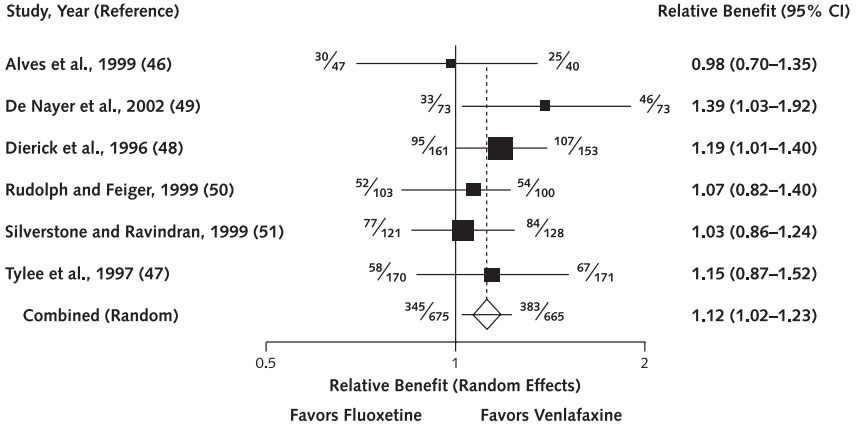
Hansen et al. (2005) systematic review:

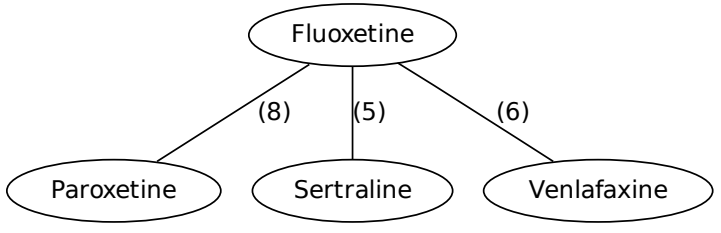
- 46 studies comparing $n = 10$ second-generation AD
- In total, 20 comparisons are available
- Out of $\frac{n(n-1)}{2} = 45$ possible comparisons
- 3 meta-analyses are performed

Meta-analysis limitations









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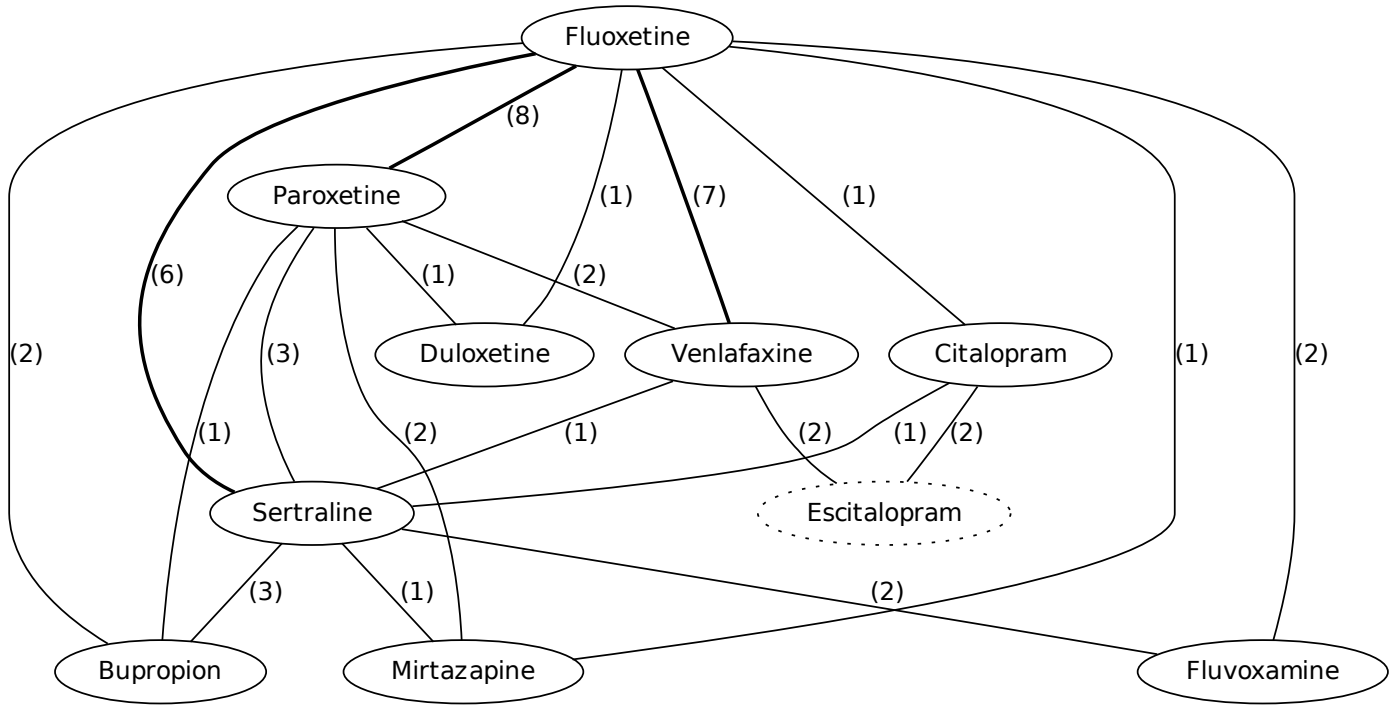
Meta-analysis limitations



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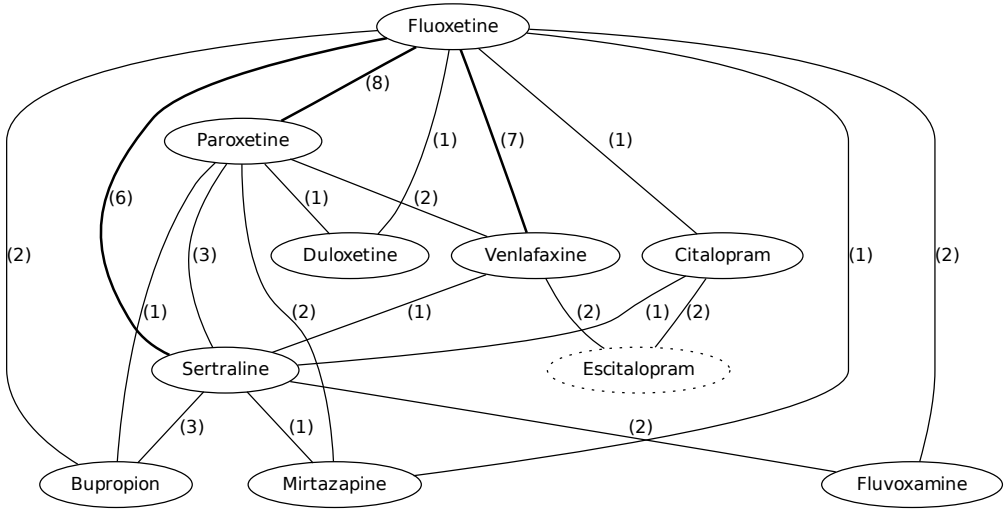
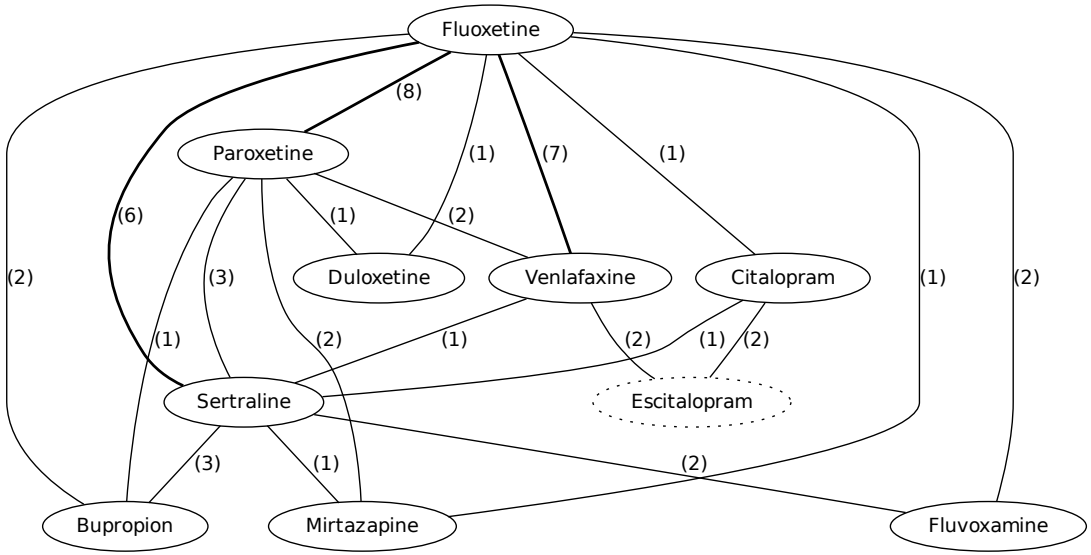


- Uncertainty about fluoxetine not represented explicitly
- What happens if we choose another baseline?
  - Other studies included $\rightarrow$ possibly different results
- Not all drugs can be included (escitalopram)
- We're "double counting" multi-arm trials

Solution: apply network meta-analysis



- Include **all** evidence in one mixed-treatment comparison (MTC) analysis
- Produce normal-distributed direct estimates instead of log-normal relative effect estimates (more justified swing weighting)

Van Valkenhoef & al., manuscript, 2010

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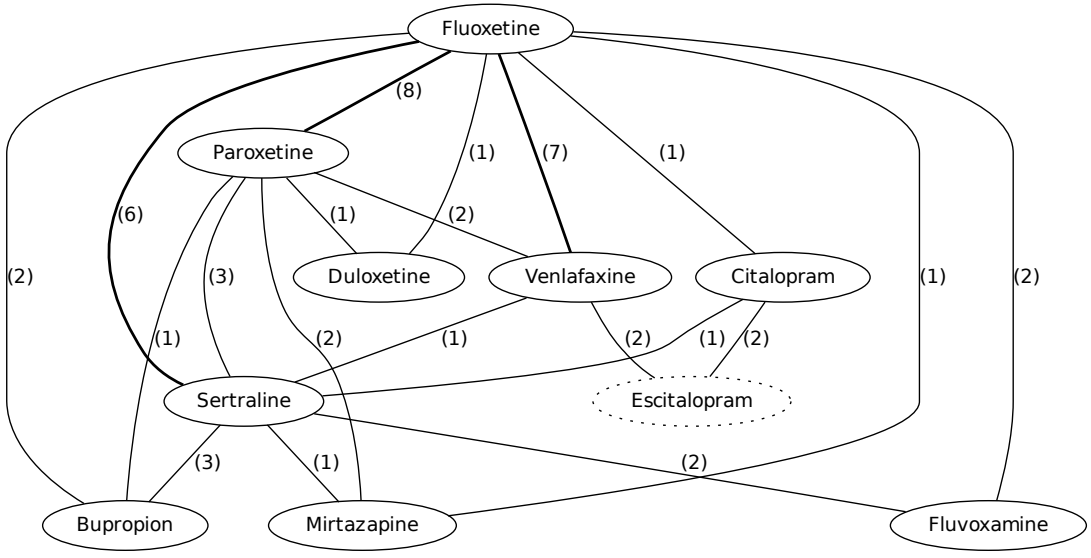
Network meta-analysis problems



- Model considerably more complex (Bayesian instead of regression)
- Treatment network inconsistency must be evaluated
- No algorithms for generating MTC models exist(ed)

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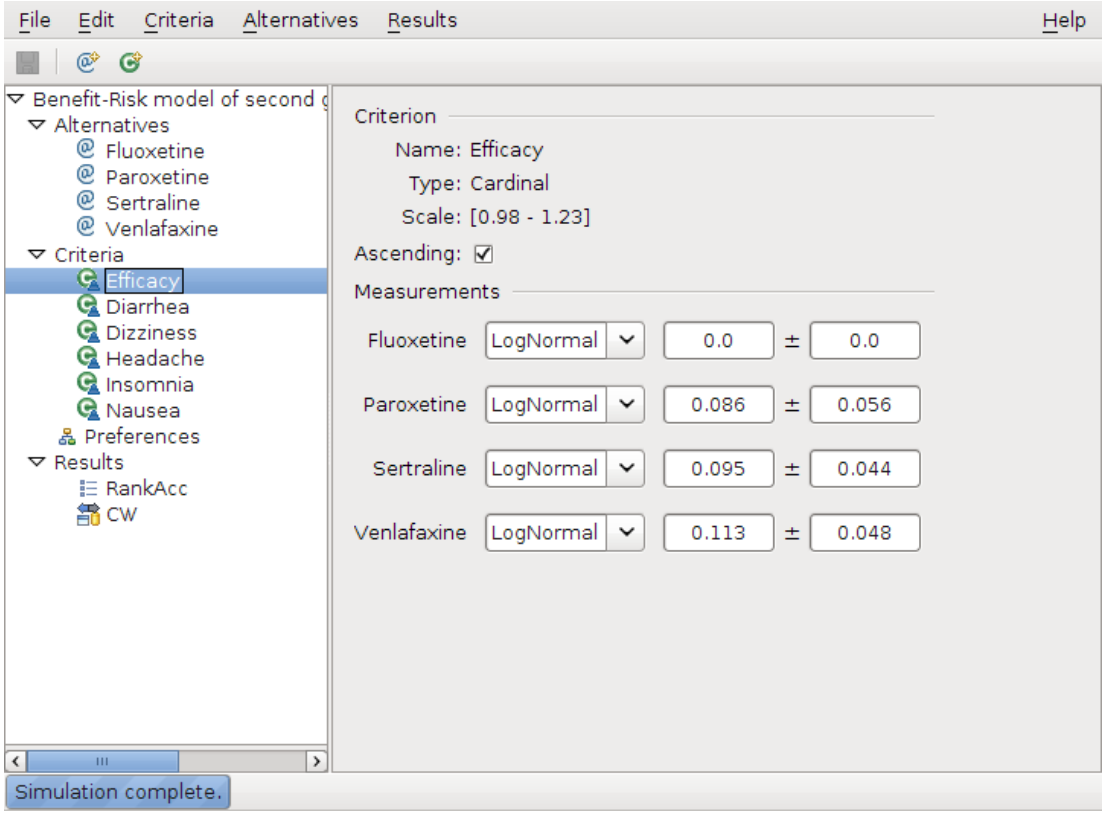
JSMAA

Main features

- Implements SMAA-{2,O,TRI}
- Save/load model in XML (close to XMCDA)
- Results visualization



http://smaa.fi

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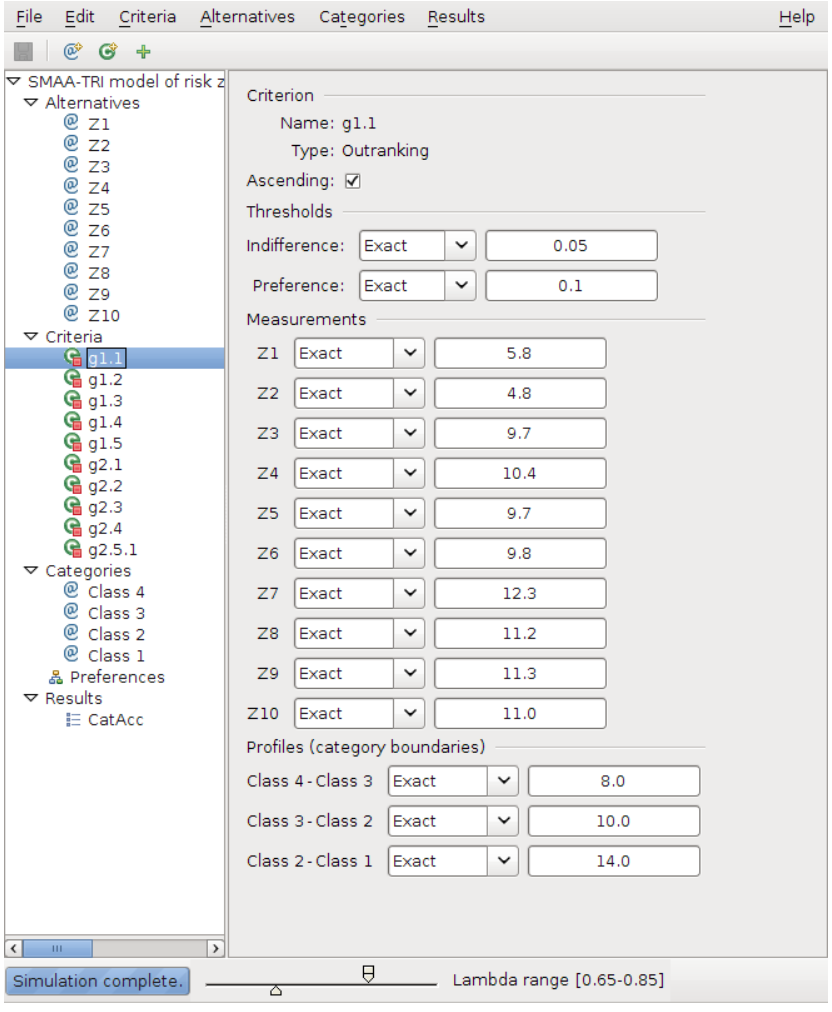

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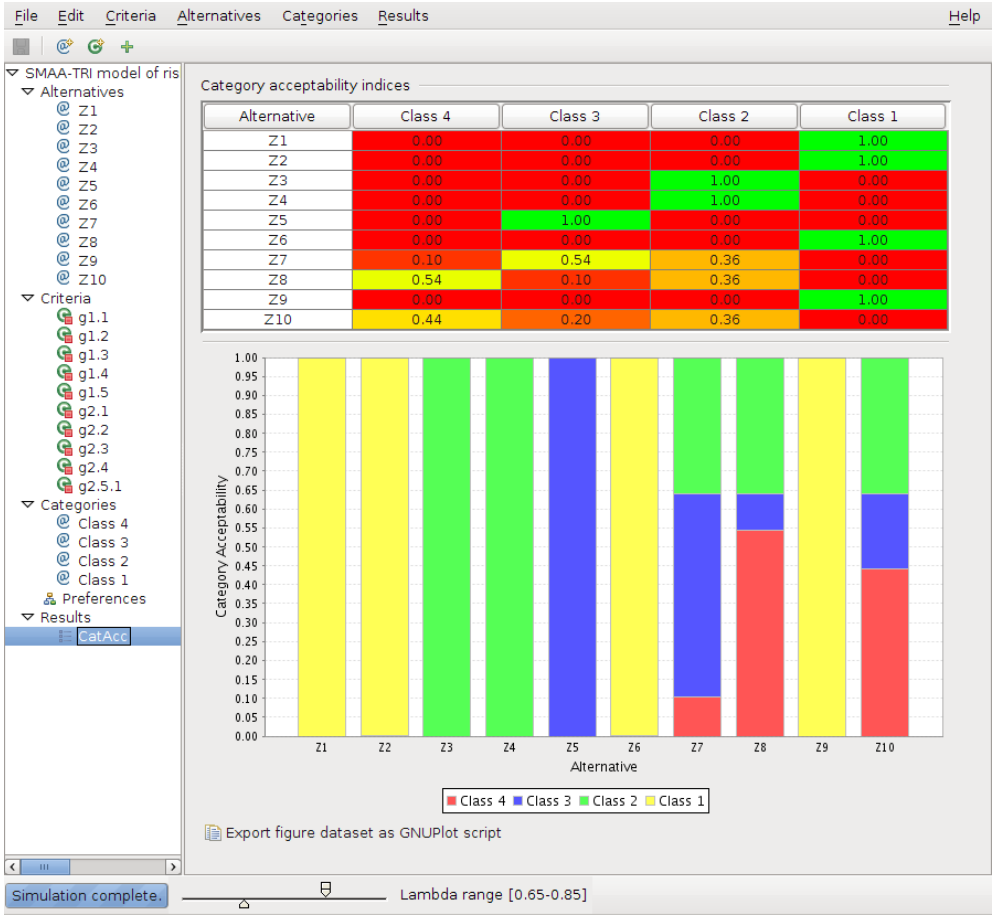

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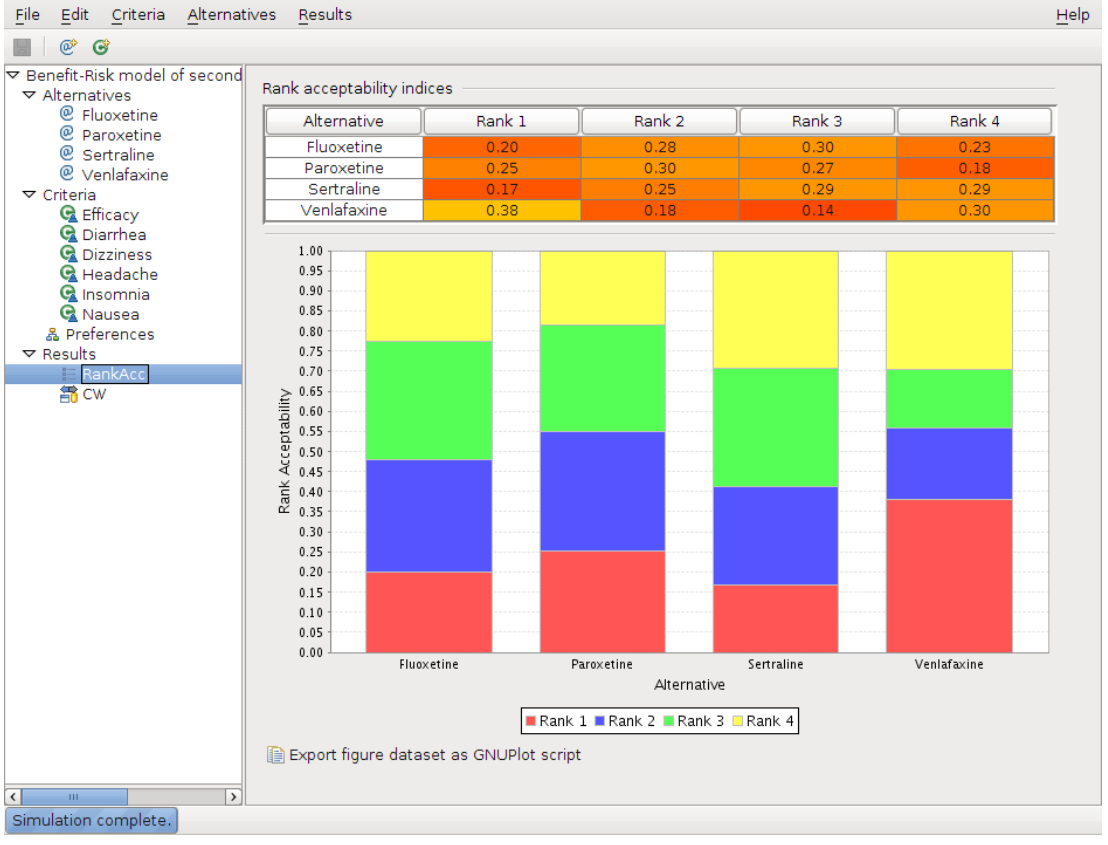

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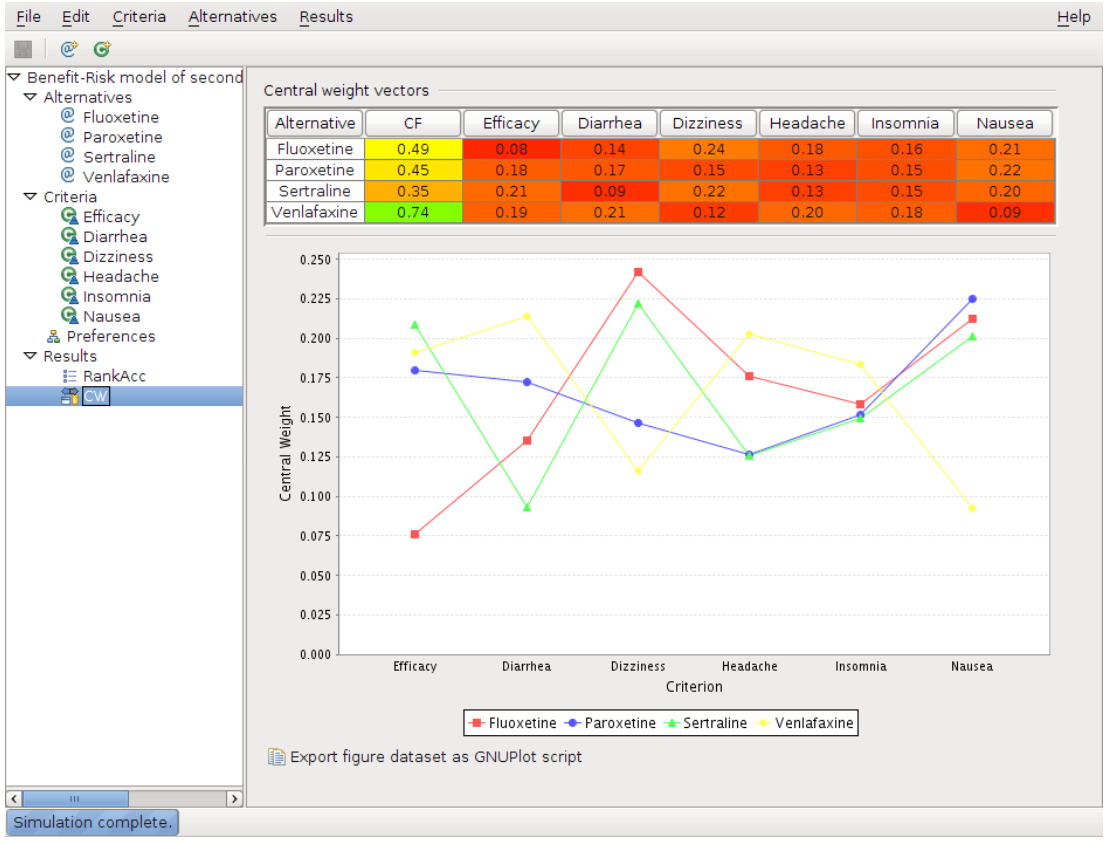
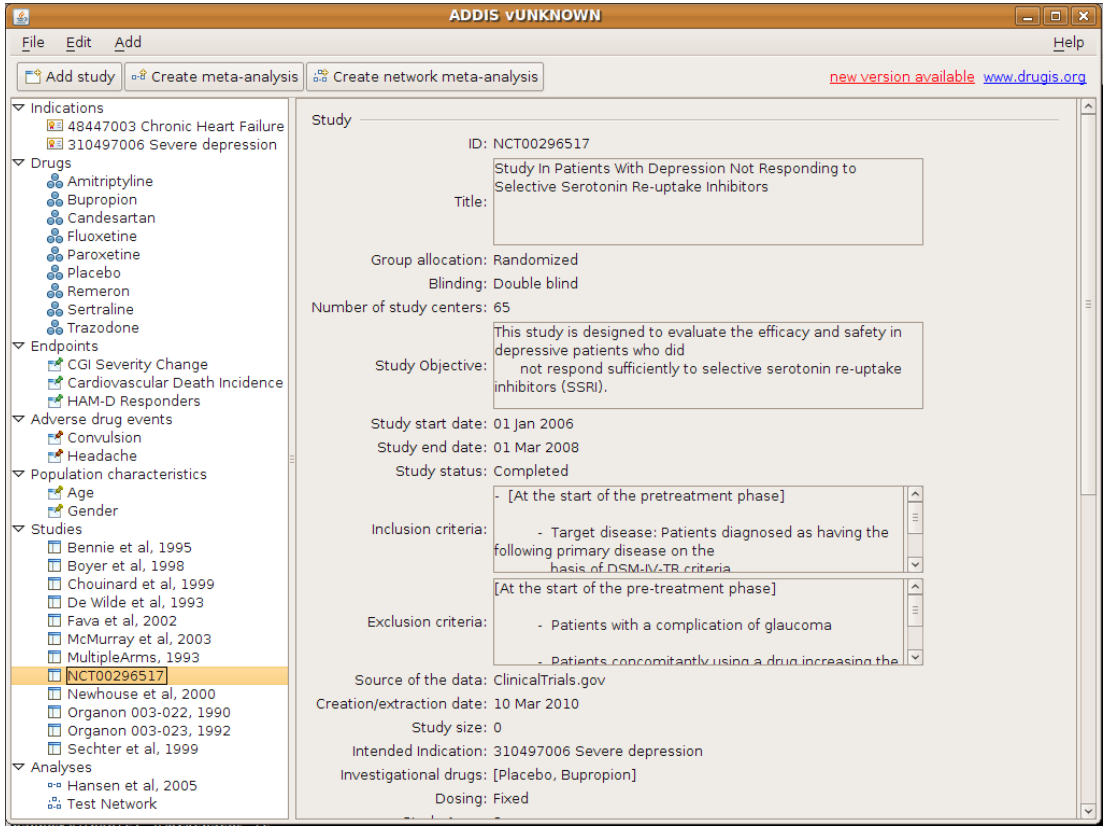


Aggregate Data Drug Information System

Main features

- Import & store trial design & results
- Generation of (network) meta-analyses
- *Generation of BR-models and their execution with JSMAA

http://drugis.org



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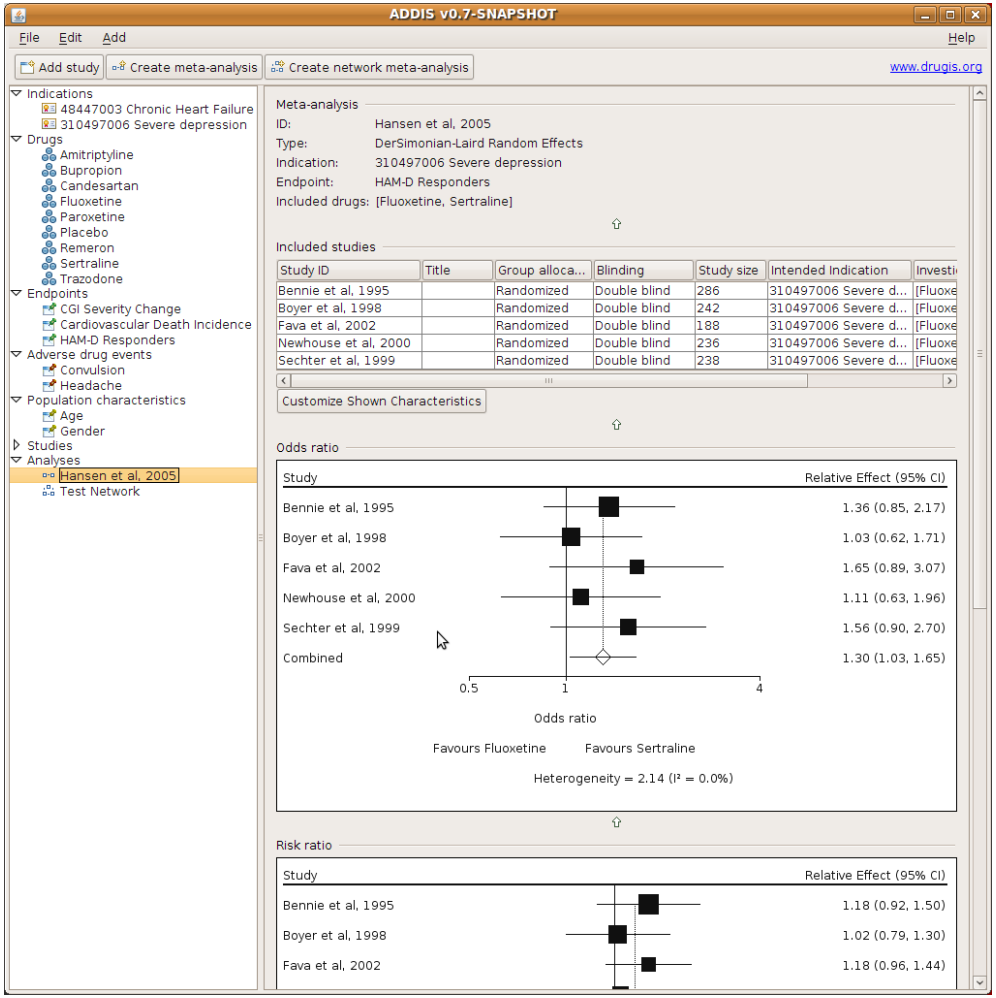

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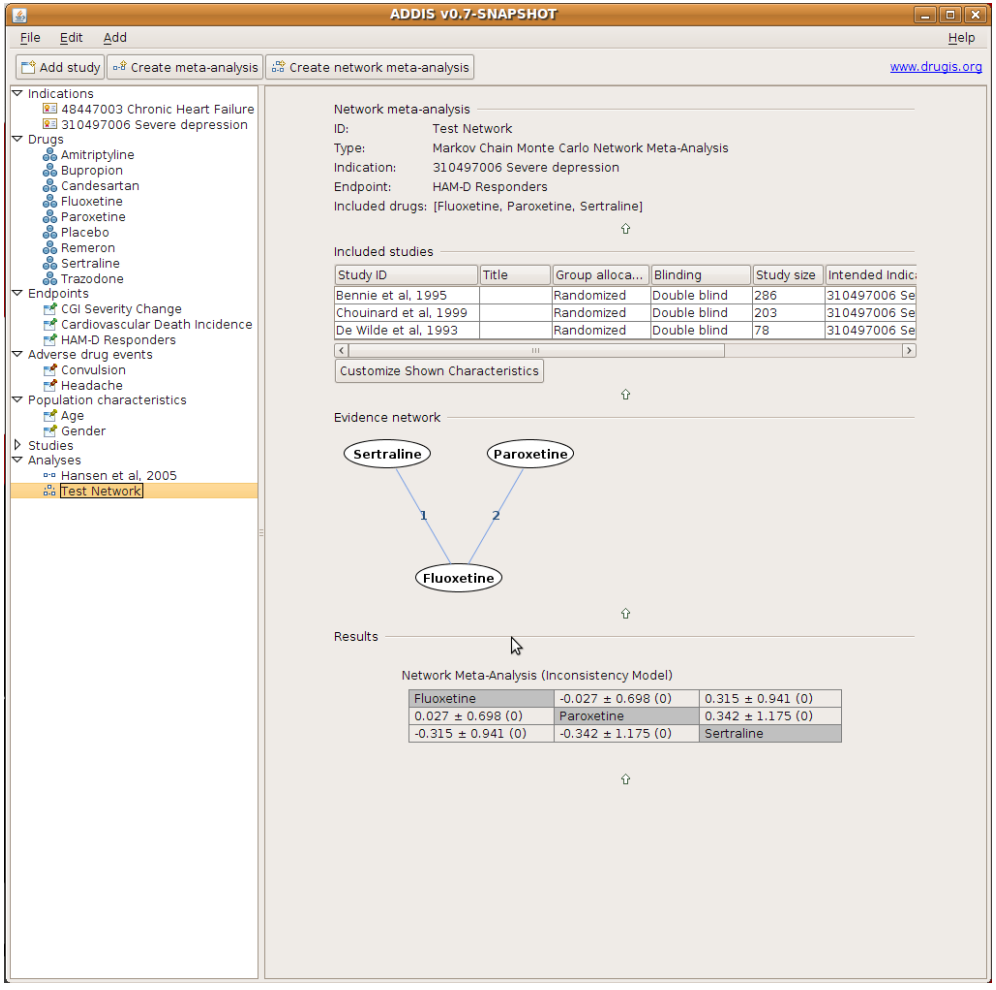

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Conclusions

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- The models can be generated semi-automatically

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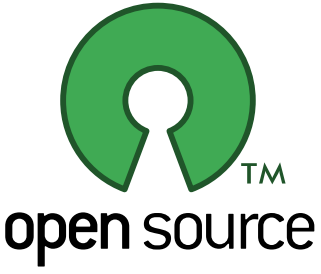
- Evidence-based medicine can be enhanced by incorporating multi-criteria decision support
- The MCDA models can take into account all relevant clinical evidence in their original format by applying SMAA+MTC
- The models can be generated semi-automatically
- We have open source software implementation of the proposed approach



Dank voor uw aandacht!

Future presentations on the topic:

- Van Valkenhoef: Multi-criteria drug benefit-risk assessment through mixed treatment comparisons. EURO 2010, Lisbon
- Postmus: SMAA-CEA: a new method for representing decision uncertainty in cost-effectiveness analysis when three or more alternatives are being compared. ECHE 2010, Helsinki
- Tervonen: Stochastic Multicriteria Acceptability Analysis (SMAA): theory, applications, and software. ALIO/INFORMS 2010, Buenos Aires
- Postmus: Using stochastic multicriteria acceptability analysis to assess the cost-effectiveness of healthcare interventions: a case study in heart failure. ALIO/INFORMS 2010, Buenos Aires

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