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The Sequential Simplex Method and Multicriteria Optimization in Analytical Chemistry

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Experiments

- We all do experiments, and we like them to give us the best possible information.
- But our goals differ:
  - scientific insight
  - better quality
  - shorter development time
  - etc
- Should we always design our experiments using the same procedure? Of course not!

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Optimization in analytical chemistry

- Separation time
- Resolution
- Absorbance
- Yield, stability
- Signal to noise ratio (S/N)
- etc.

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Direct optimization vs. model-building

- Direct optimization
  - Many experimental factors, but few experiments
  - Sequential
  - Simple, cheap and quick
- Model-building
  - Few experimental factors, but many experiments
  - Run in batch
  - Costly, take a lot of time, but give scientific insight

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Where to start?

- Choice of ”tools” depend on the problem,
- but direct optimization should always be considered to be a part of the strategy!
- Why?
- To quickly find exactly where to put the experiments.
  - This is of critical importance if we are to run ”screening” experiments to choose ”important” factors.

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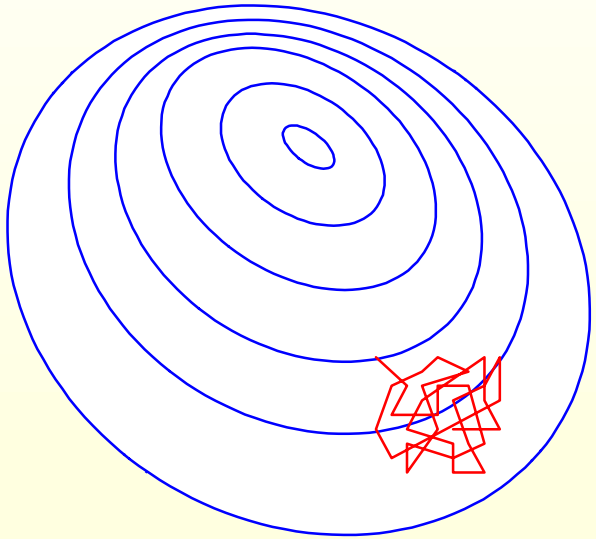
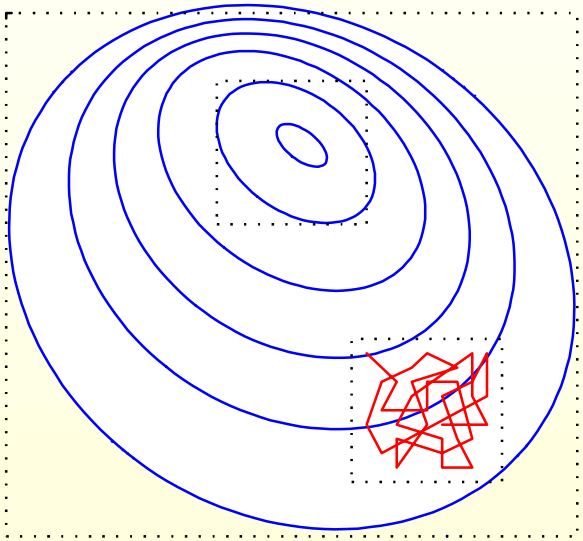
Where to start? cont.





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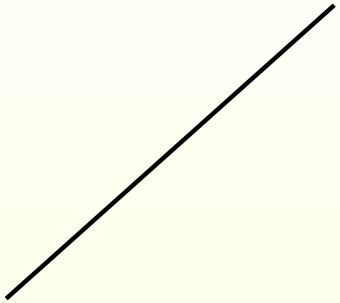
The simplex methods

- The basic simplex method
- The modified simplex methods
  - Nelder & Mead, with modifications
  - Super modified
  - Weighted centroid
  - Composite modified
  - Etc

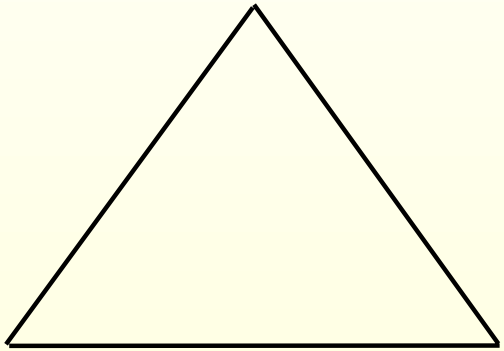
The simplex methods cont.

- Easy to understand and apply.
- Initial k+1 trials, a ”simplex”.
- Subsequent trials in the direction of improvement.
- Method characteristics:
  - Sequential.
  - No assumption about an underlying model.
  - Cost-effective, few trials compared with RSM.

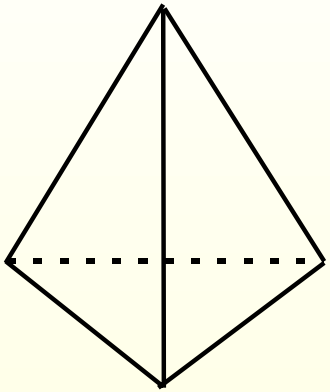
A simplex



1D, a line



2D, a triangle



3D, a tetrahedron

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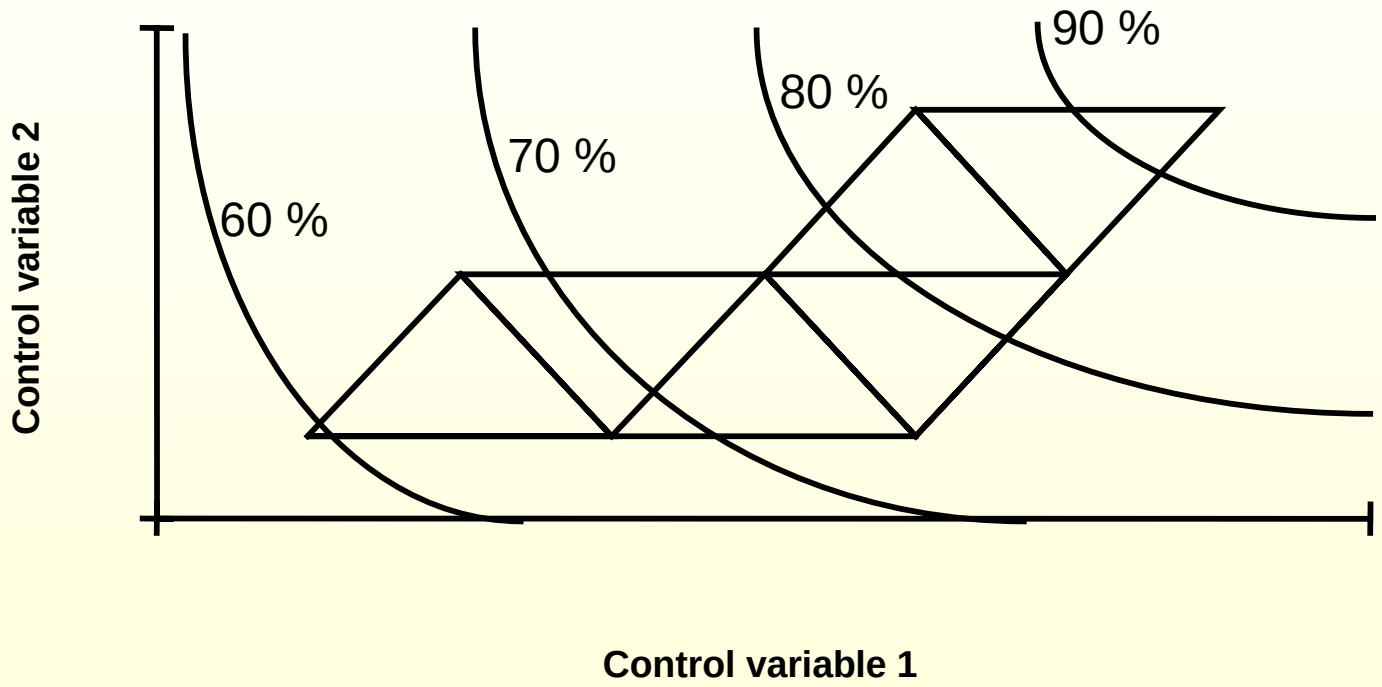
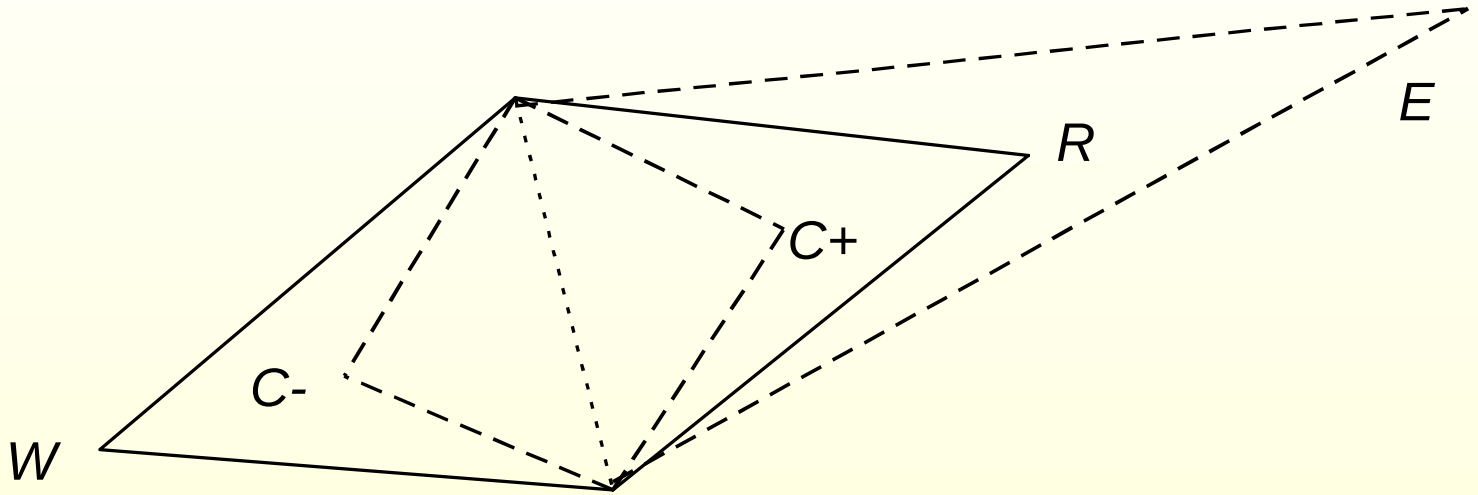
The basic simplex method



The modified simplex method



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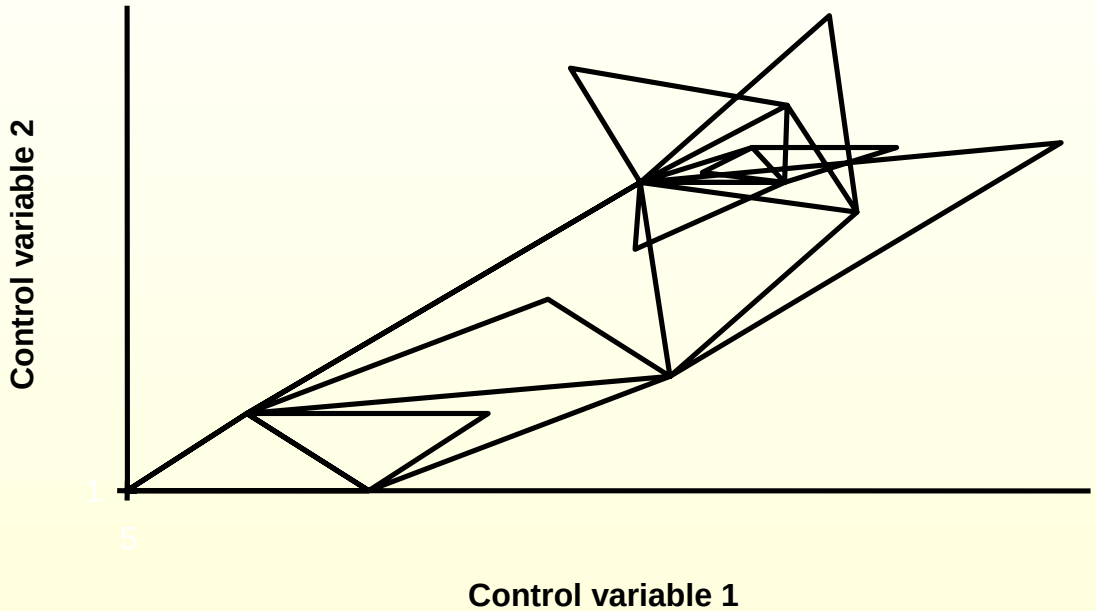
The mod. simplex method cont.



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Applications & literature

- Use within analytical chemistry was popularized by S. N. Deming and co-workers in the 1980s.
- More than 400 publications on appl. in chemistry (mainly analytical chemistry).
- Several text books, e.g. *Sequential Simplex Optimization* by F.H. Walters et al
- Many reviews on applications in analytical chemistry, e.g. Deming (1978), Rózycki (1993) and Walters (1999).

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Applications & literature cont.

- Spectroscopy
  - UV-VIS
  - AAS
  - ICP
- Chromatography
  - GC
  - LC
  - TLC
  - HPLC
- Flow injection methods
- Electrochemistry
- Titration
- Extraction
- XRF, MS, NMR, etc.

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Multicriteria optimization

- We often have several responses to optimize simultaneously.
- Multicriteria optimization is therefore a balancing act, e.g. separation time and resolution.
- ”Desirability” or ”fuzzy set membership functions” is a useful approach.

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Multicriteria optimization cont.

- The response variables are measured with different scales.
- The relative significance of different variables differ.
- For some response variables the objective is maximization, but for others it is minimization or a specific target.

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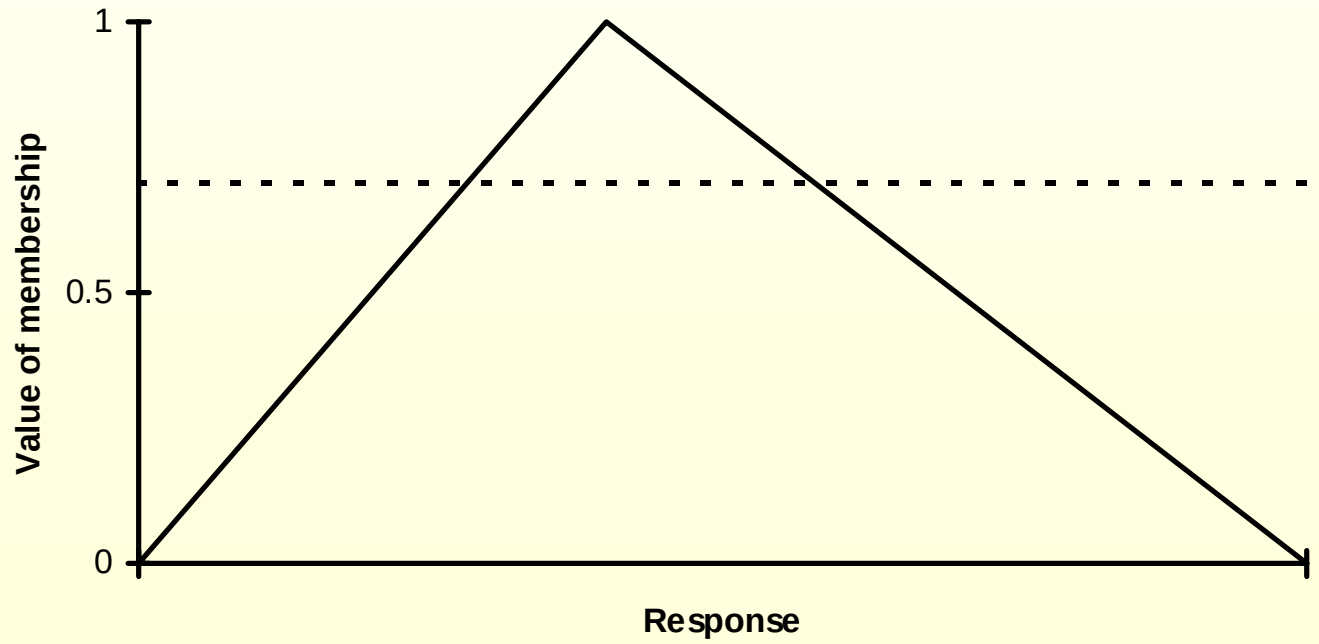
Multicriteria optimization cont.

With membership functions, the objective (i.e. target) is represented by a chacteristic function varying between 0 and 1.



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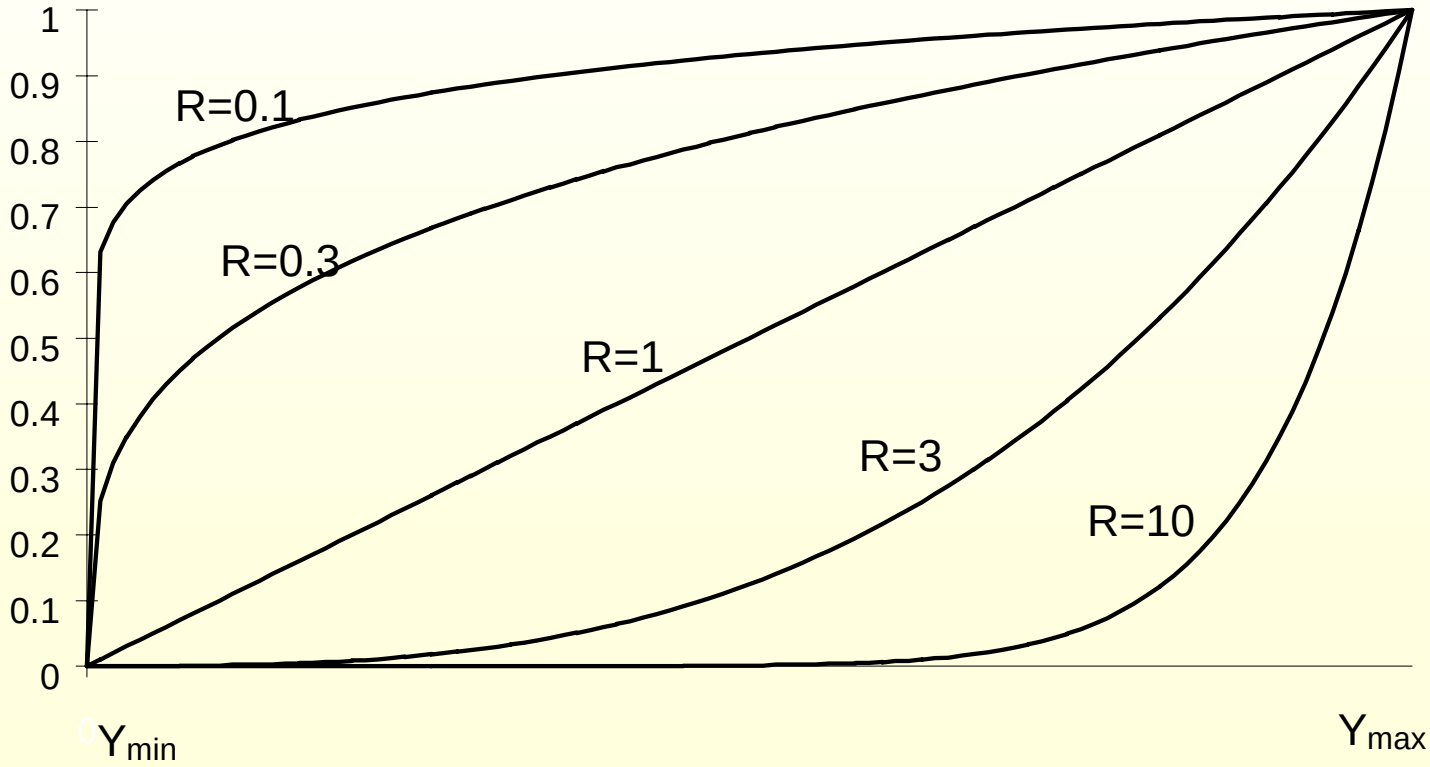
Multicriteria optimization cont.

Different shapes, $f(x)=x^R$



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Multicriteria optimization cont.

The aggregated membership:

$$M(y) = \left[m(y_1)^{\beta_1} \times m(y_2)^{\beta_2} \ldots . \times m(y_i)^{\beta_i} \right]^{\frac{1}{\Sigma \beta_i}}$$

- *M(y)* = the aggregated value of membership.
- *m(yi)* = the membership value for the individual response variable.
- β_i = the influence value for the individual response variable.
- *I* = the number of response variables.

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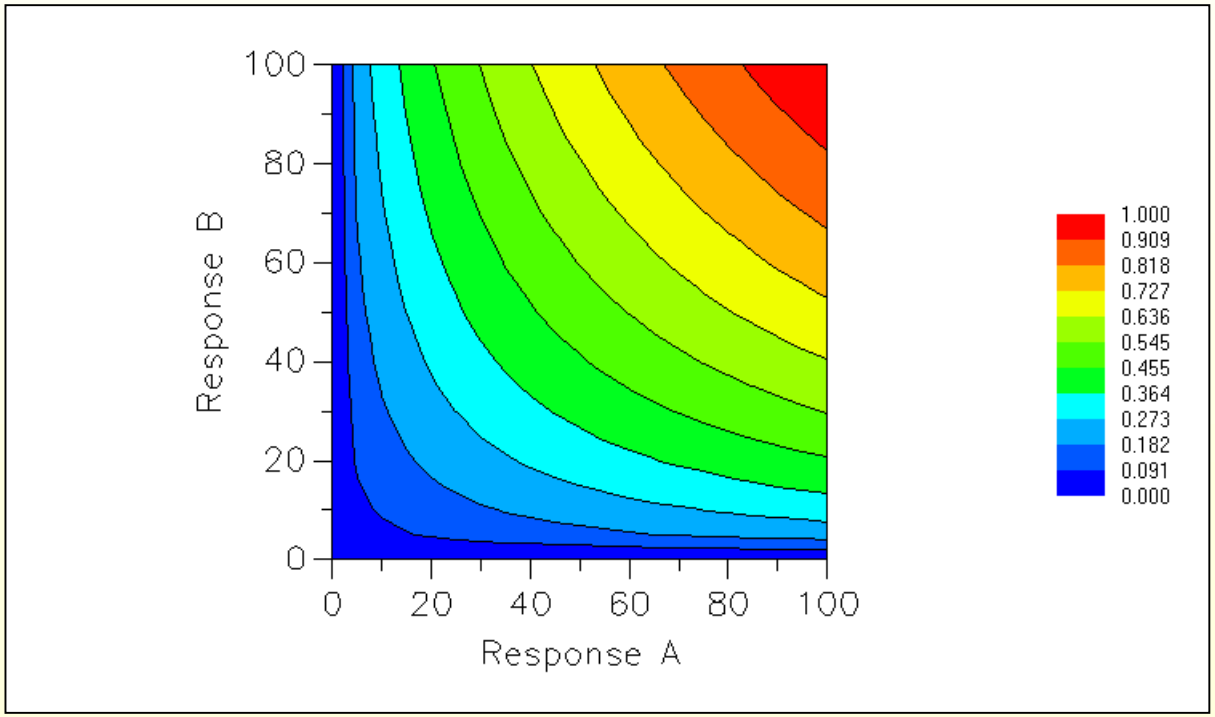
Multicriteria optimization cont.

The aggregated membership (ex. maximization):



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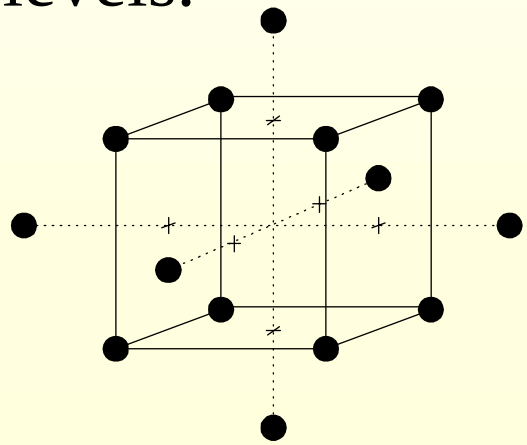
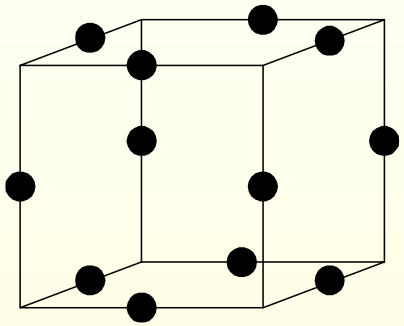
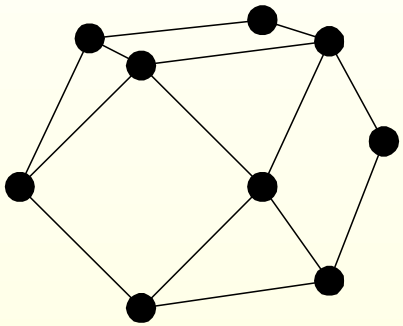
Comparison of methods

Classical experimental design, i.e. response surface methodology (RSM).

Experiments at min. three factor levels.







No. variables	*3*	*4*	*5*	*6*
Box-Behnken	15	27	46	54
Central Composite	23	36	59	100

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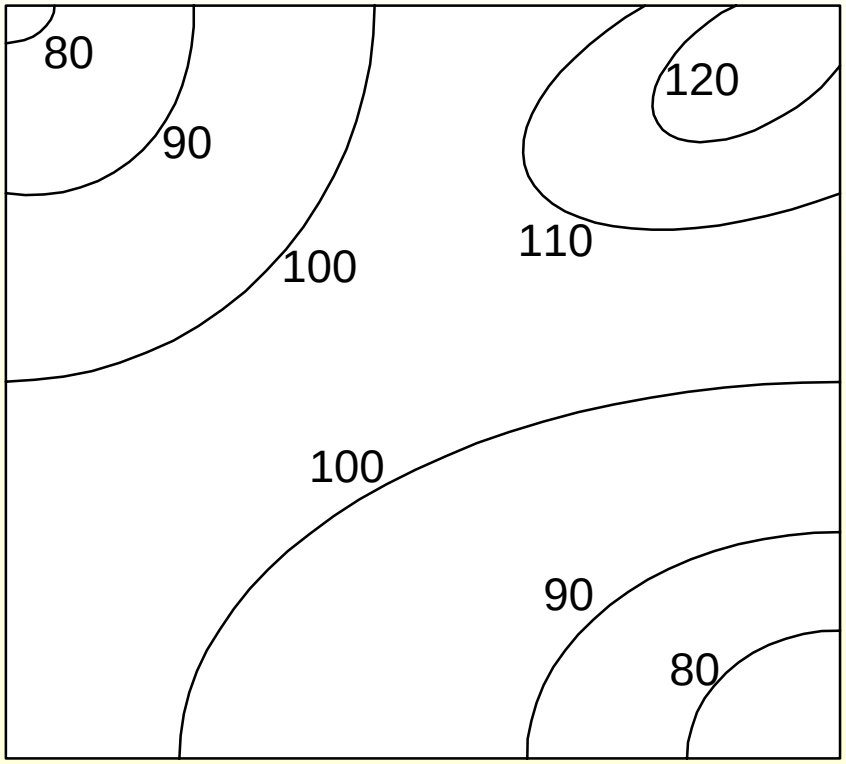
Comparison of methods cont.

- A polynomial is fitted to the experimental data.
- The model can be visualized with e.g. contour plots.
- Several responses can visualized in ”overlay plots”.

$$y = b_0 + \sum b_i x_i + \sum b_{ii} x_i^2 + \sum \sum b_{ij} x_i x_j + e$$



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Comparison of methods cont.

- Simplex
  - Pros
    - Quick and easy
    - Cost-effective
    - Sequential
    - No model assumptions
    - Many experimental variables
  - Cons
    - Sequential
    - Data not suitable for model-building
- RSM
  - Pros
    - Optimal for modelling
    - Scientific insight
    - Batch-wise
  - Cons
    - Time-consuming
    - Costly (many experiments)
    - Batch-wise
    - Few experimental variables

Comparison of methods cont.

- Ask the right question
  - What is the purpose? Optimization or scientific insight?
    - Optimization: Use simplex!
    - Model-building: Simplex + RSM!
- The simplex will assist to locate the best experimental domain!

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A case study

- Problem
  - To optimize a HPLC method for analysis of a pharmaceutical product.
- Experimental variables
  - pH, ACN% and temperature.
- Response variables
  - Resolution x 3
- Software: MultiSimplex®

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A case study cont.

pH	ACN, %	Temp., °C	Rs 12	Rs 23	Rs 34
4.75	16.5	42.5	0.5583	1.343	1.884
4.75	15.5	47.5	0.897	1.508	2.007
5.25	15.5	42.5	0.7992	2.132	0
5.25	16.5	47.5	0.5351	1.42	0
4.58	15.2	40.8	0.6888	2.937	1.879
4.25	14.5	37.5	0.6492	0	0
4.14	15.9	44.7	0.5692	0	0
4.97	15.6	43.1	0.7596	1.179	2.299
4.79	14.4	45.1	1.108	1.3	2.657
4.44	14.4	45.9	1.009	3.408	2.048
4.18	13.8	47.3	1.27	4.53	2.017

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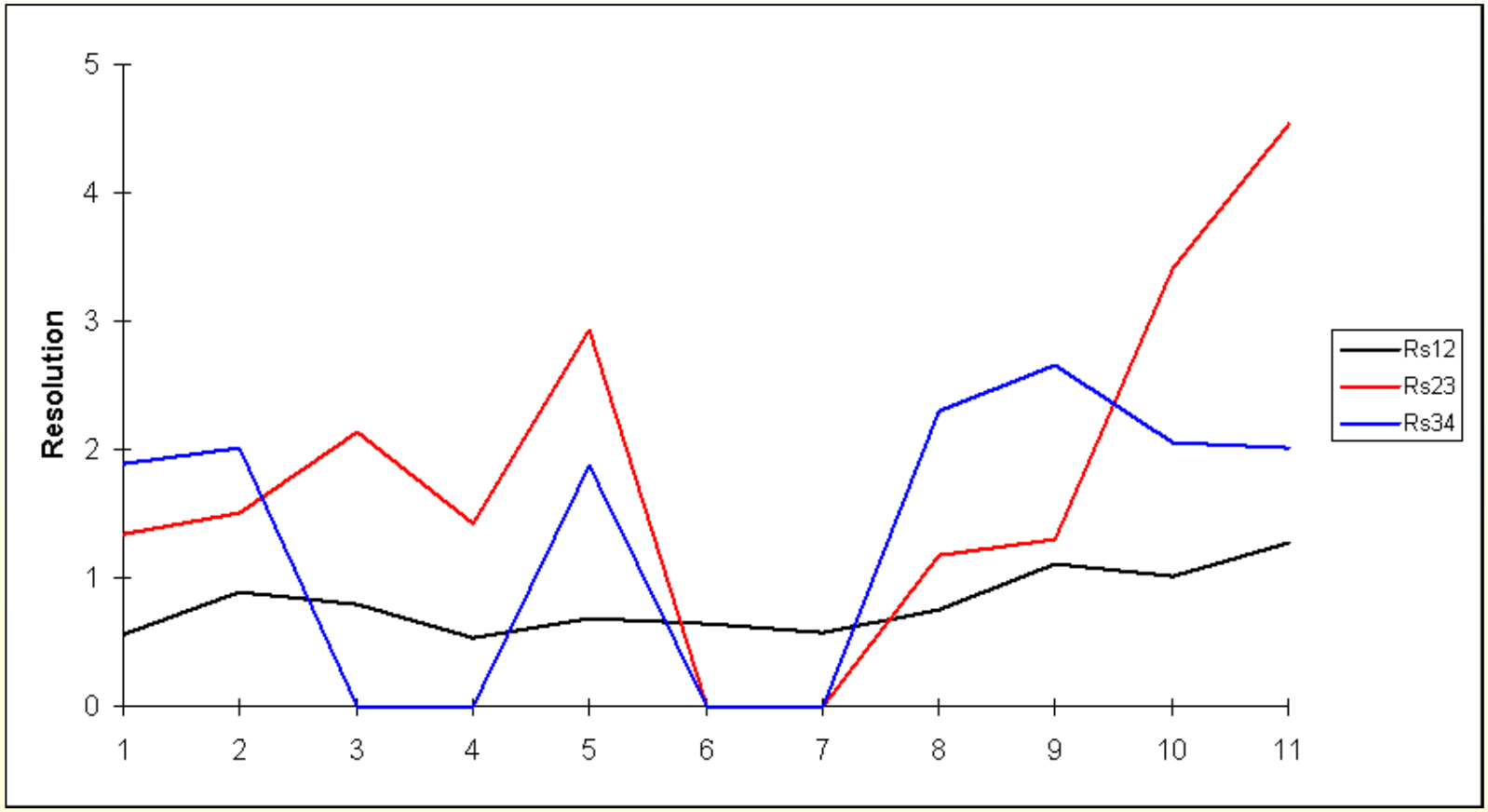
A case study cont.



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A case study cont.

- The HPLC-method for this pharmaceutical product was improved significantly.
- Some additional trials are needed to ensure that the optimal conditions are found.
- The problem is solved in an quick and easy way by using simplex and membership functions for experimental optimization.

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Conclusions

- The sequential simplex method has proved to be very effective for optimization of many different analytical methods.
- Literature, application notes, and a demo is now freely available over the Internet.
- A commercial software tool is also available for free evaluation.
- This *"...has speeded up the acceptance and use of simplex optimization"*. (F. Walters, 1999)

Acknowledgement

- It is impossible to talk about simplex optimization without mentioning the pioneering work by prof. Stanley N. Deming and coworkers in the 1980s. Their work have provided us with inspiration and ideas in the development of the MultiSimplex® software.
- I am also grateful to one of our customers in the pharmaceutical industry for providing the experimental data for the case study.