Uncertainty from validation studies

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What is Measurement Uncertainty?

"A parameter, associated with the result of a measurement, that characterises the dispersion of the values that could reasonably be attributed to the measurand"

(ISO Guide)

The number after the ±

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ISO Guide approach

- Specify the measurand
  - including complete equation
- Quantify significant uncertainties in all parameters
  - A: from statistics of repeated experiment
  - B: by any other means (theory, certificates, judgement...)
- Express as standard deviation
- Combine according to stated principles

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Implementing ISO in Chemistry
Building models

- Every determinand is unique
  - Every element, every molecule, every formulation
- Every ‘matrix’ is unique
  - Different interactions with substrate
- Interactions with environment and substrate rarely understood
- Models are difficult to build!

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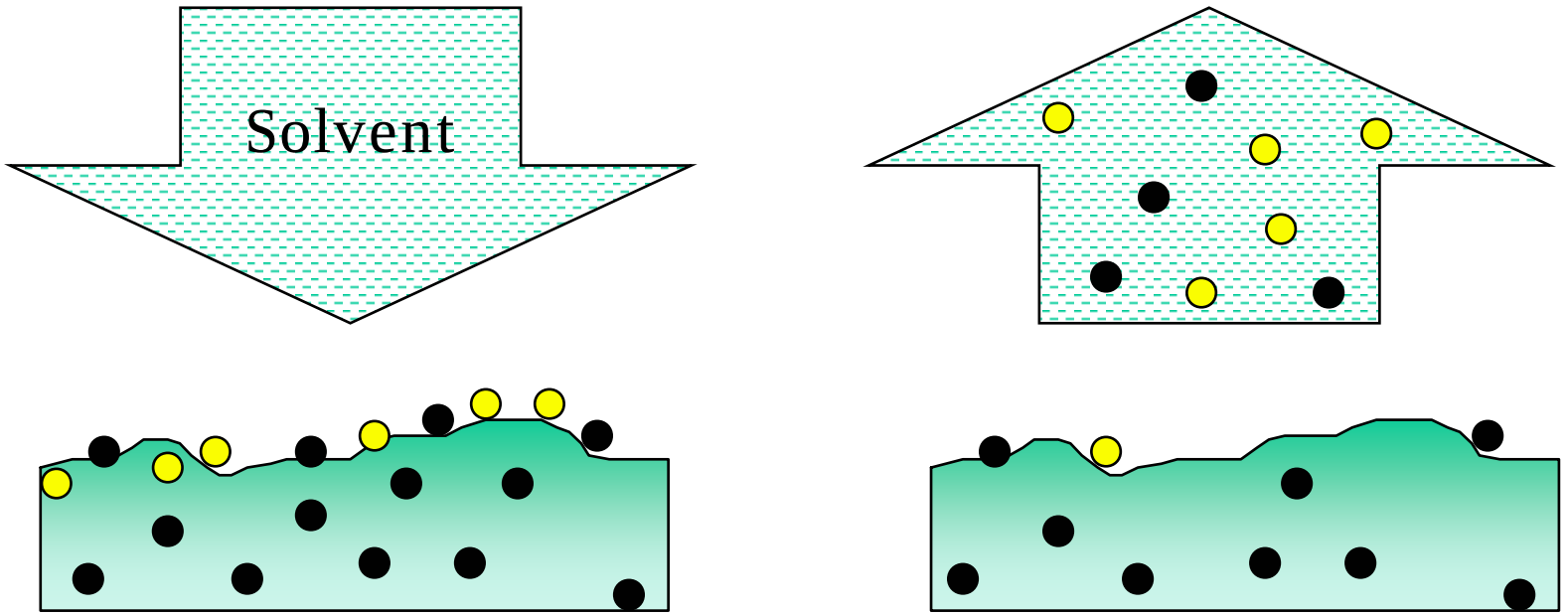
Extraction processes



● ‘Incurred’

○ Added reference

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A simpler model

- The best available estimate of precision
  - *An effect varied representatively during a precision experiment requires no further study*
- The best available estimate of bias *and its uncertainty*
- Other significant effects evaluated
  - By experiment, or from standing data

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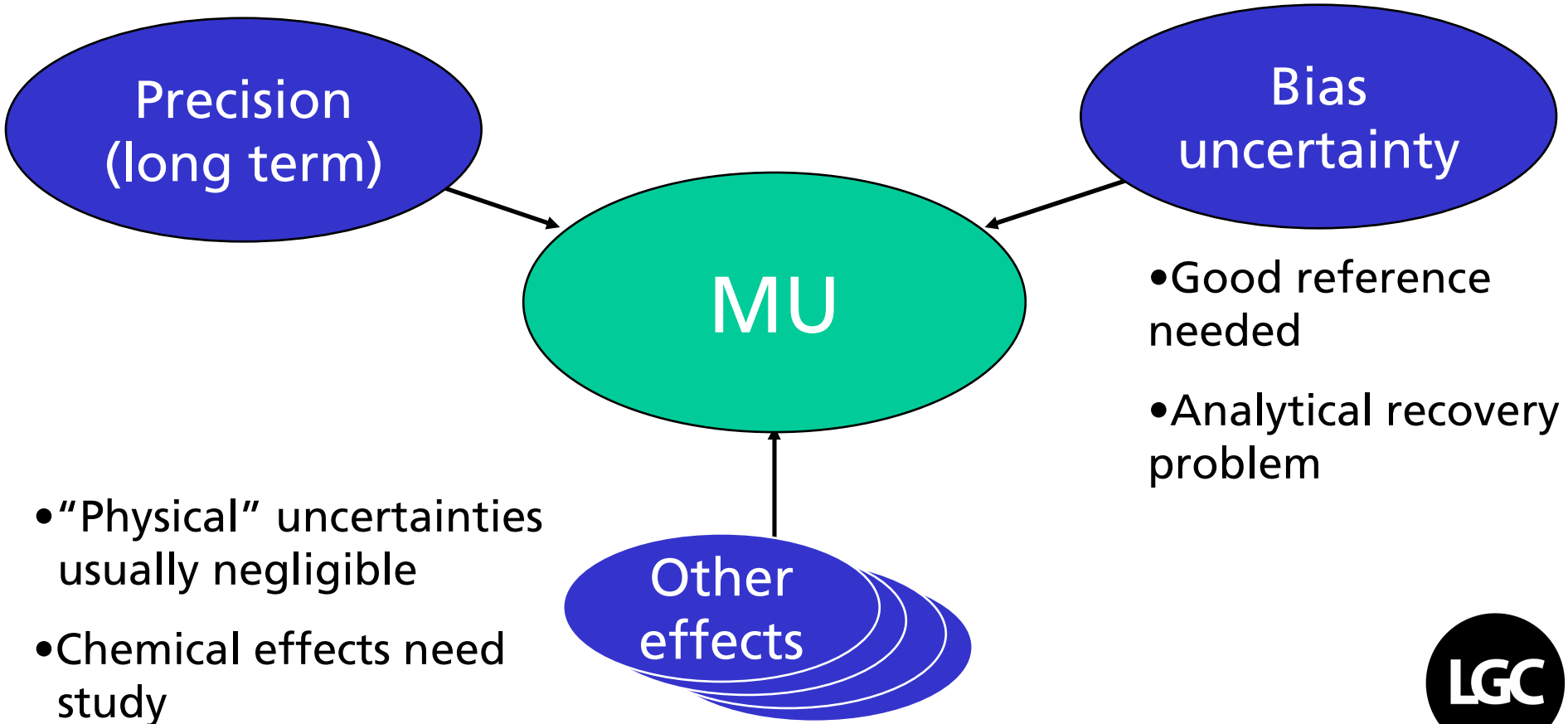
In-house validation



- Good reference needed
- Analytical recovery a problem

- "Physical" uncertainties usually negligible
- Chemical effects need study

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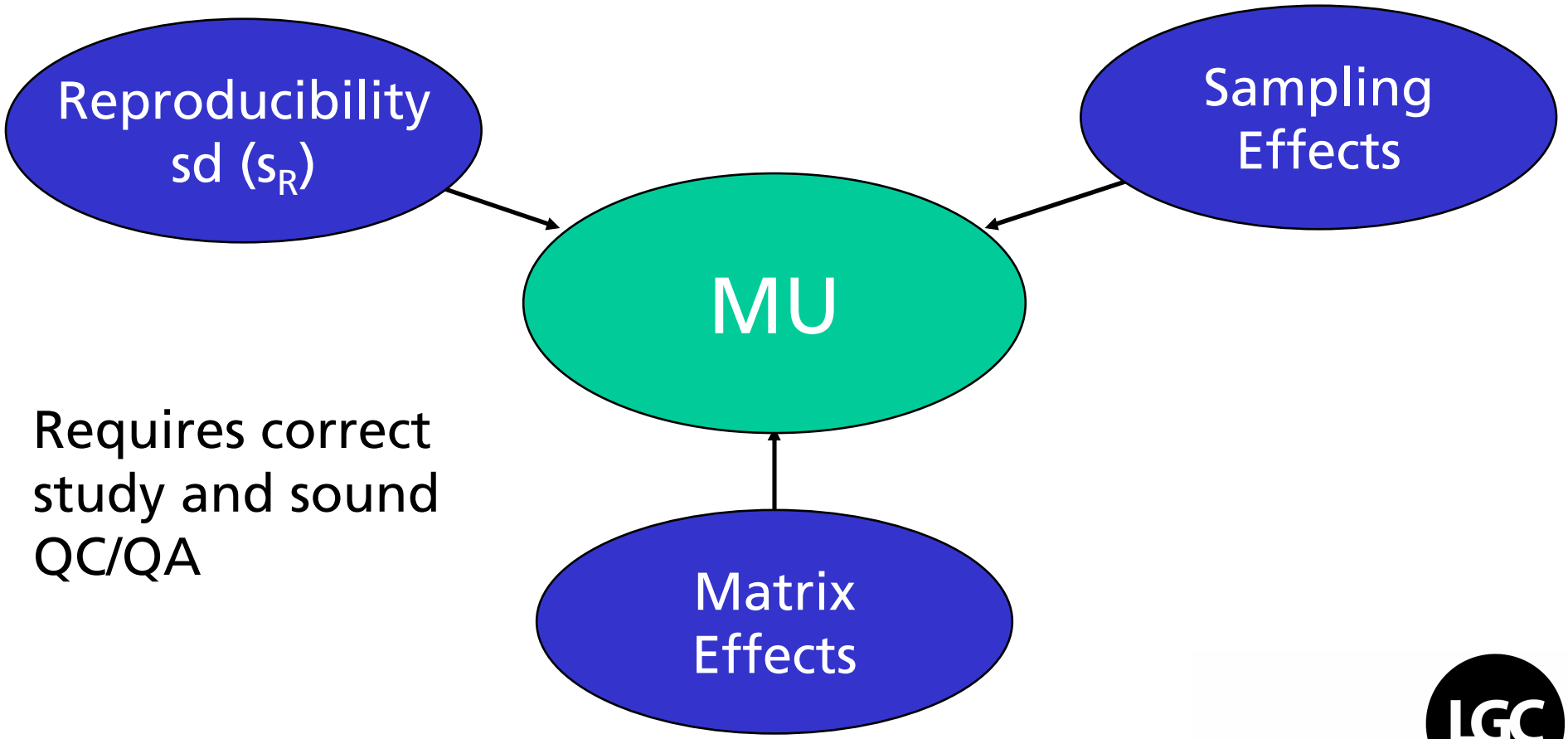
Collaborative Study



Requires correct study and sound QC/QA

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Experiments for measurement uncertainty estimation

- Random variaton
- Recovery studies
- Other effects
  - Simple sensitivity analysis
  - Numerical calculations
  - Response surfaces

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Random variation

- Standard deviation of replicate measurements;
- Results of ANOVA
  - within- or between-group standard deviation;
- Significance tests;
  - in a t-test the denominator can be interpreted as a standard uncertainty.

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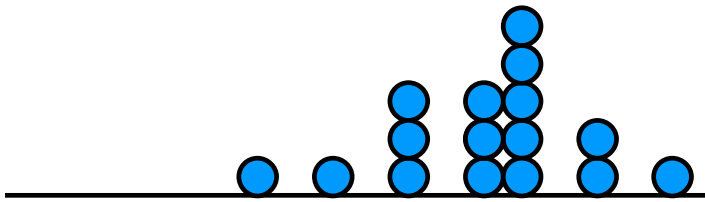
Standard deviations



$$s = \frac{\Sigma\left(x_i - \bar{x}\right)^2}{n-1}$$

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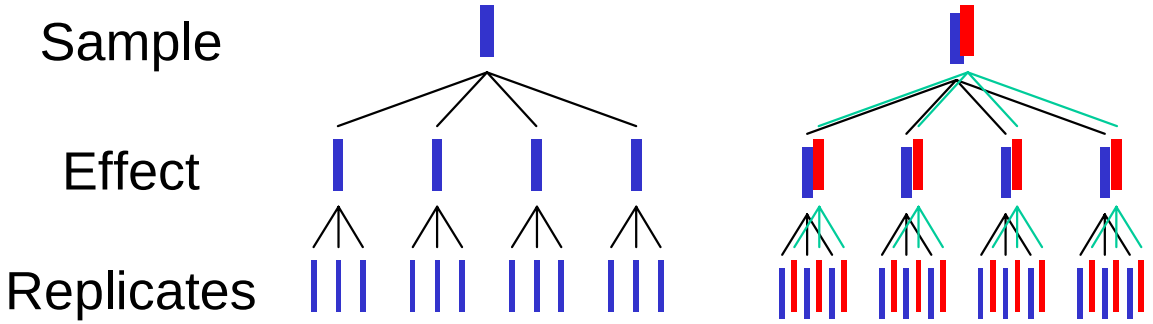
ANOVA variance components



Source of variation	SS	df	MS
Between groups	…	…	MS_B
Within groups	…	…	MS_W
Total	…	…	…

$$s_{within} = \sqrt{MS_W} \qquad s_{between} = \sqrt{\frac{MS_B - MS_W}{n}}$$

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An approach to Recovery uncertainties

$$y_{corr} = y_{obs} \times R_m \times R_s \times R_{rep}$$

R_m corrects for mean reference recovery

R_s is a nominal correction for 'sample effects'

R_{rep} corrects for spike recovery differences

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Uncertainties in Recovery estimates

- Reference value uncertainty
  - Traceability Uncertainties - *Small*
- Measurement on reference value
  - Repeatability dominated: *Small*

R_m

- Relevance of reference to sample
  - *LARGE unless matrix-specific RM*

R_s

- Spike behaviour
  - *LARGE in most heterogeneous systems.*

R_{rep}

see *Analyst* **124** 981-990 (1999)

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Evaluating $u(R_m)$

- With representative CRM or reference method:
  - Analysis of CRM *or* with reference procedures:
    $u(R_m)$ from stats and certified uncertainty
- Without representative CRM
  - Spiking studies: *$u(R_m)$ as above, but needs $u(R_{rep})$*
  - Changes in extraction system, 'worst case' CRM:
    $u(R_m)$ from extreme values
  - Recovery behaviour monitoring/modelling:
    $u(R_m)$ from model

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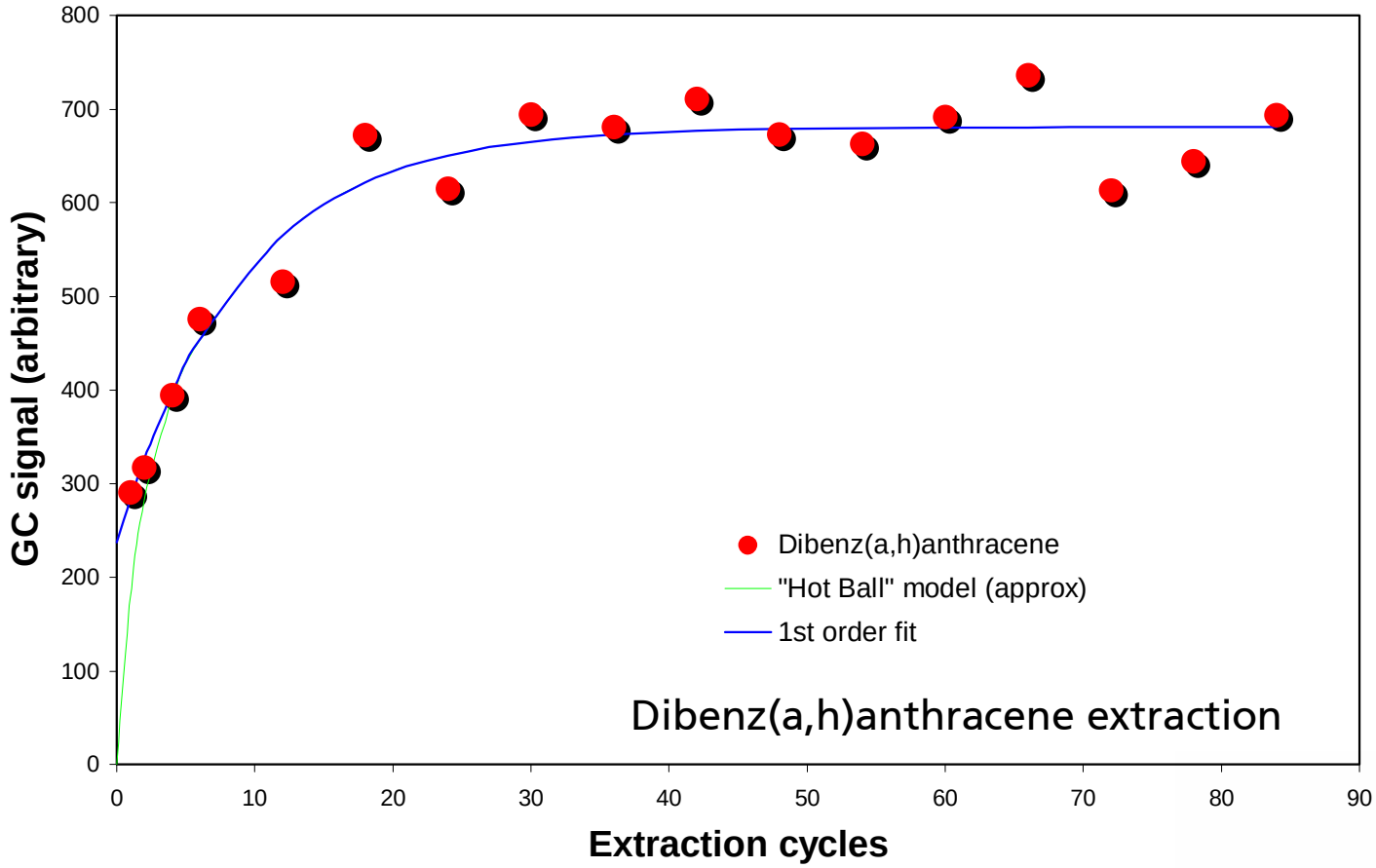
Characterising Extraction Behaviour



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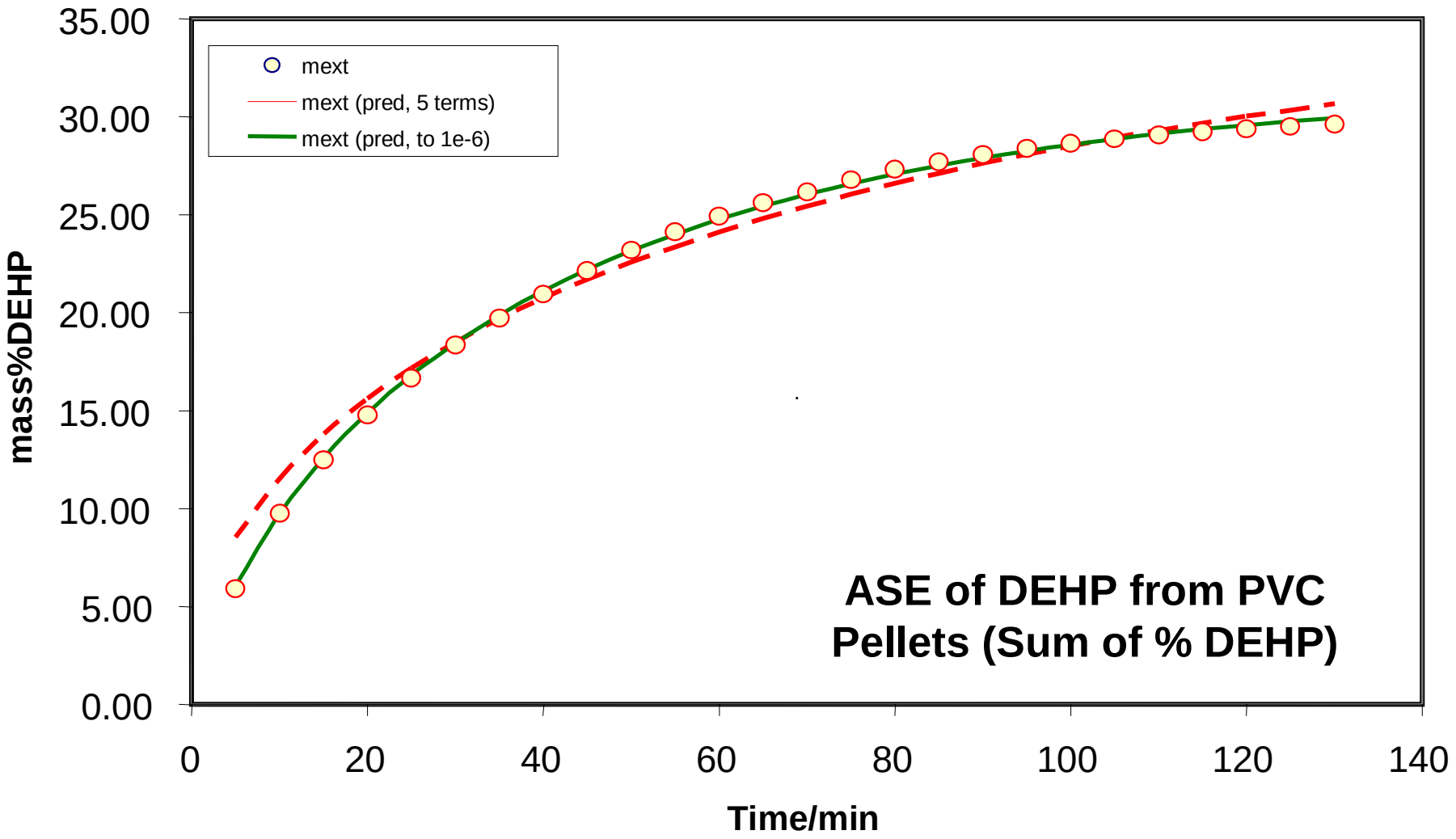
Improving technology



Evaluating $u(R_s)$
('sample effect')

- Replicate analysis of range of CRMs
  - *or* Comparison of results with standard procedures
  - $u(R_m)$ from statistical observation and certified uncertainty
- Spiking studies on range of materials
  - u(Rm) as above, but needs $u(R_{rep})$
- NB: Some intricate equations*

*V. J. Barwick, S. L. R. Ellison

Analyst, 1999, 124, 981-990.

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Evaluating $u(R_{rep})$
(representativeness of spiking)

- Analysis of spiked CRM(s)
- Behaviour of similar materials
- Monitoring & modelling extraction rates (native vs spiked)

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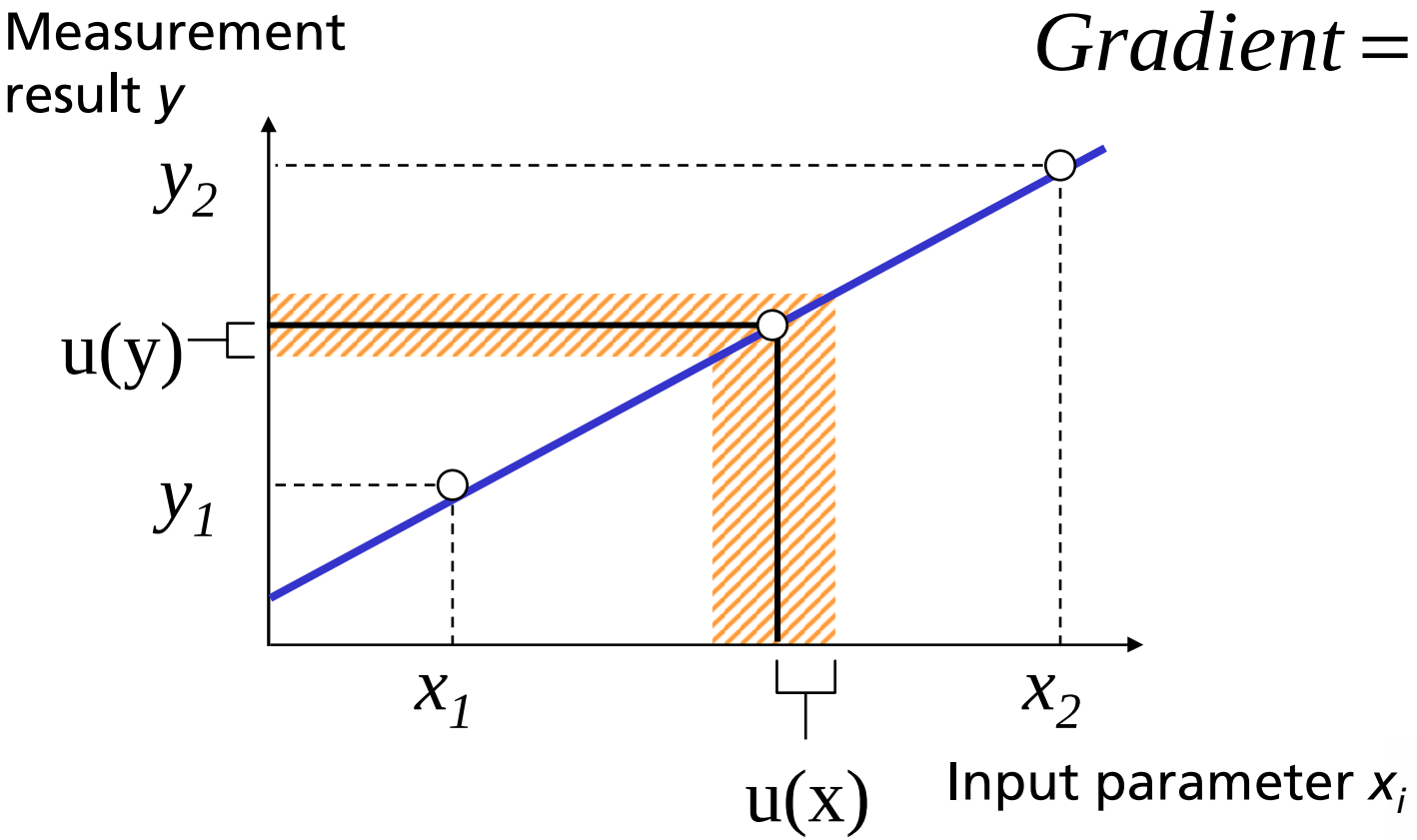
Other effects: A simple uncertainty experiment

$$Gradient = \frac{(y_2 - y_1)}{(x_2 - x_1)}$$



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Sensitivity analysis: Crude Fibre analysis

Dietary Fibre: Summary of contributions to the measurement uncertainty		
Parameter		**Uncertainty***
Precision	u(P)	0 · 0265
Acid concentration	$u(conc_{acid})$	0 · 0003
Alkali concentration	$u(conc_{alkali})$	0 · 00048
Acid digestion time	$u(time_{acid})$	0 · 01
Alkali digestion time	$u(time_{alkali})$	0 · 0072
Drying temperature and time	u(dry)	0 · 115 %(w/w)
*all the uncertainties are quoted as relative standard deviations except for u(dry)		

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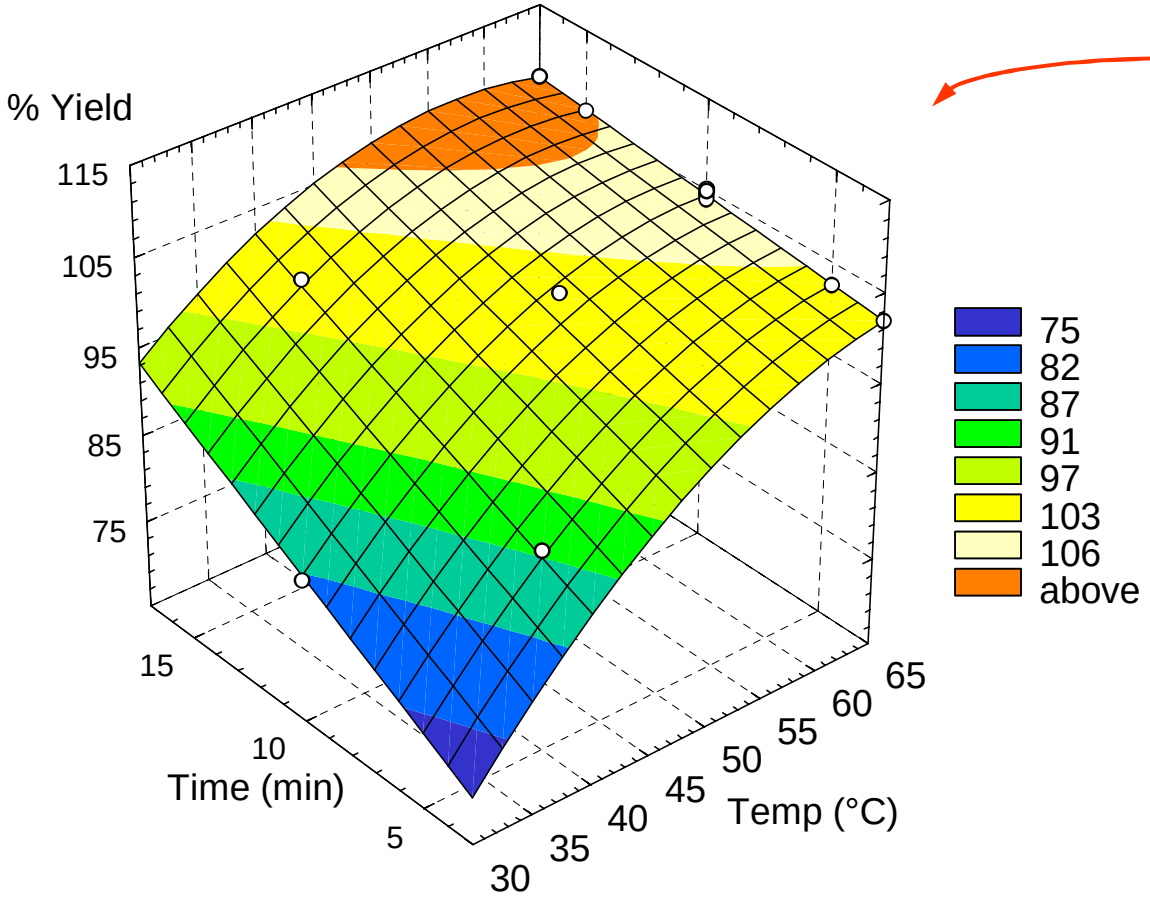
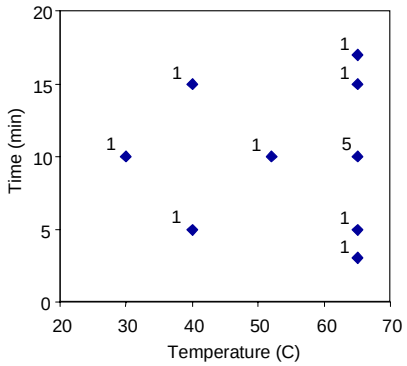
Response surface modelling

Triglycerdide saponification





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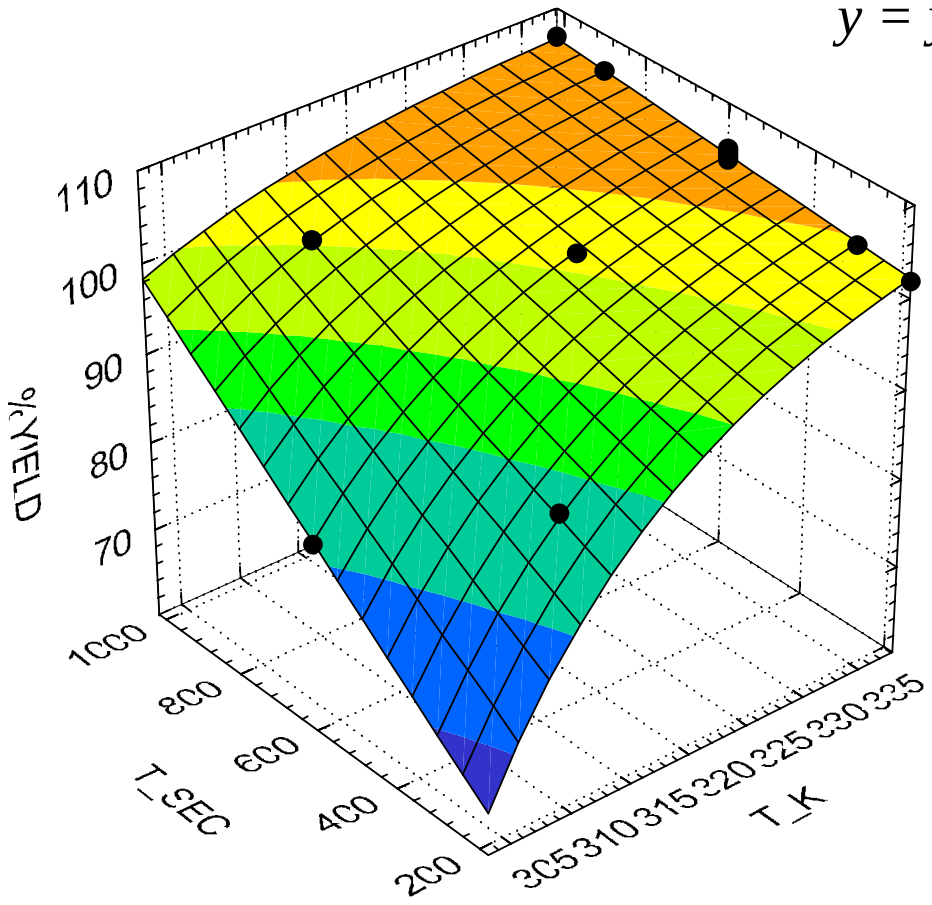
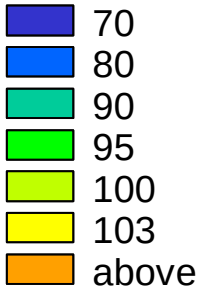
Improved model



$$y = y_0 + a_T \exp(-k_T/T)$$

$$+a_{Tt}\, t.\exp(-k_T/T)$$

(Empirical 'kinetic form')



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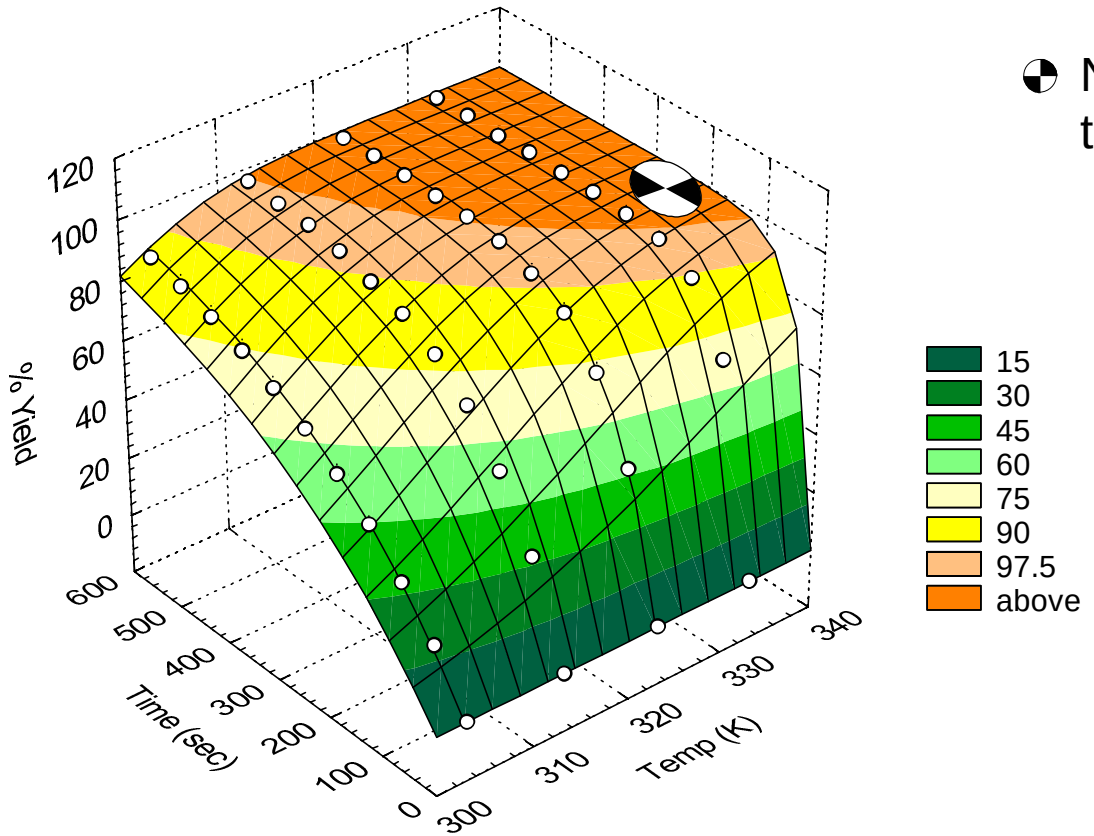
Full kinetic study

C18:2 - acid-catalysed methylation



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Modelling and experimental studies

- Sparse (eg verification) data may give inappropriate fitting
- Chemical knowledge helps - but models may be more complex
- Uncertainty estimates broadly insensitive to models if they fit the data well.
- The most useful information may be evidence of negligible contributions!

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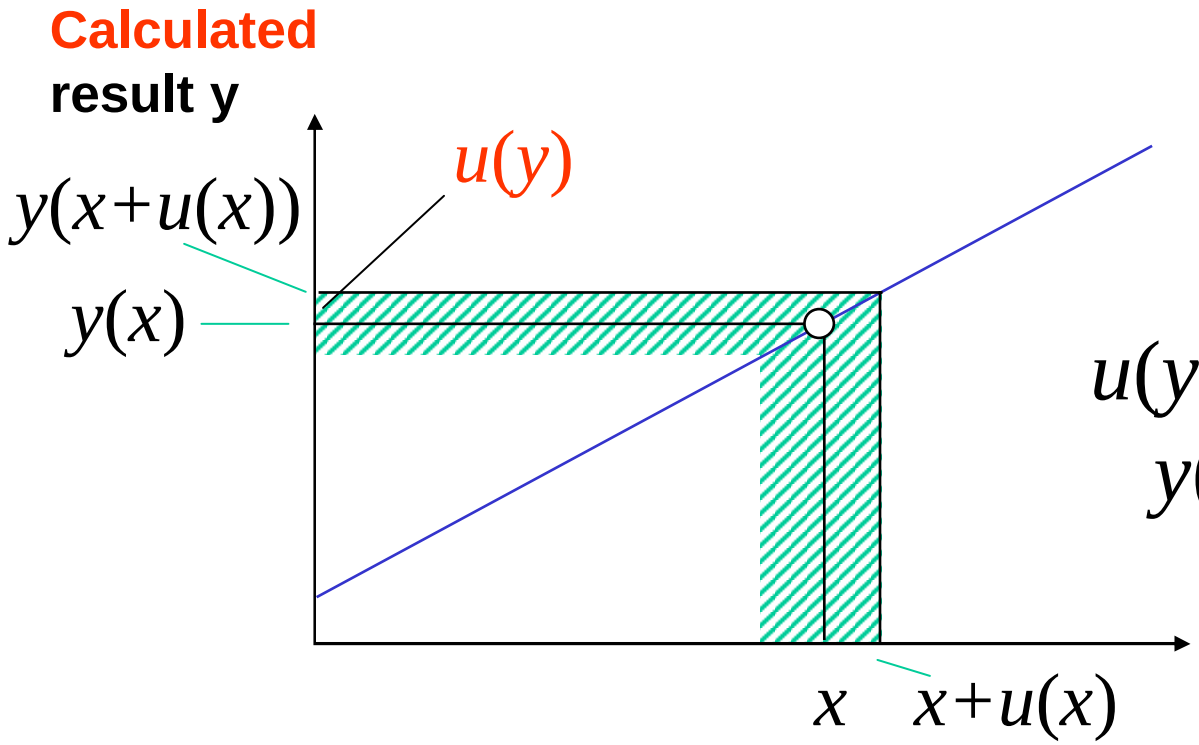
Numerical calculation



$$u(y) \approx y(x+u(x)) - y(x)$$

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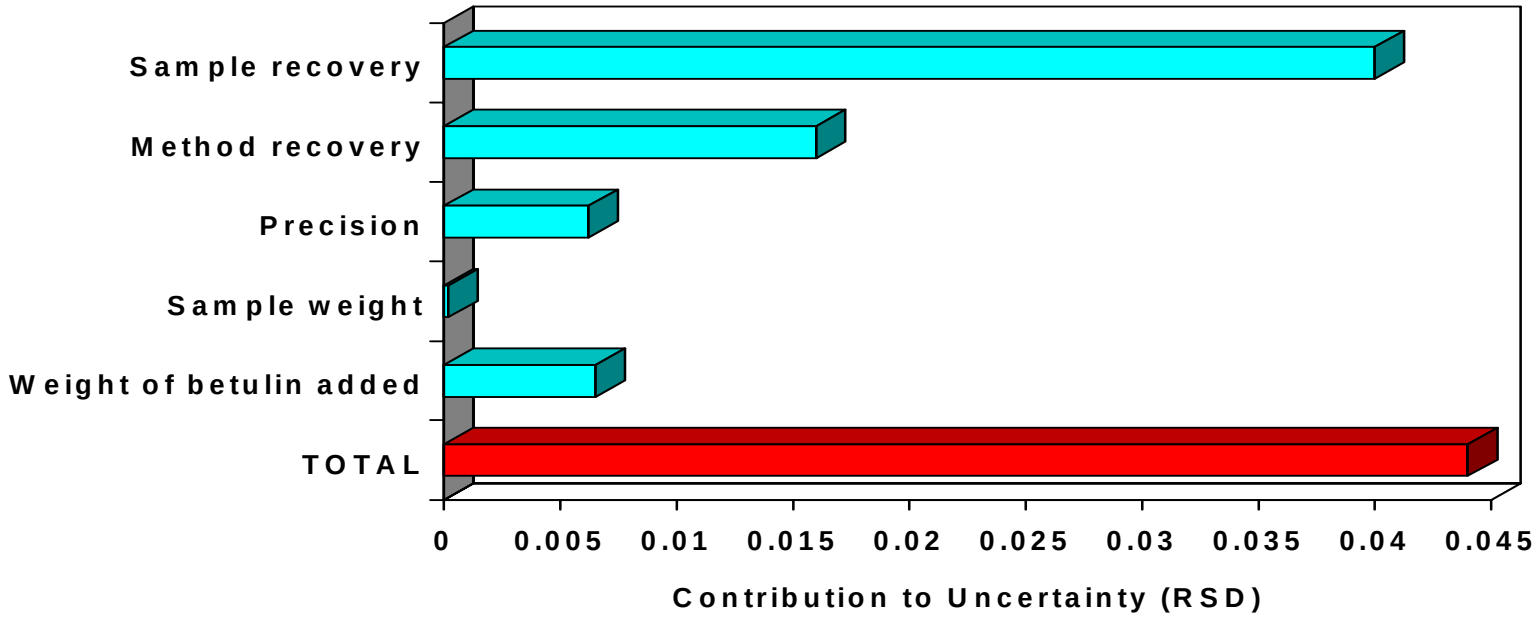
Uncertainty Components

Determination of Cholesterol



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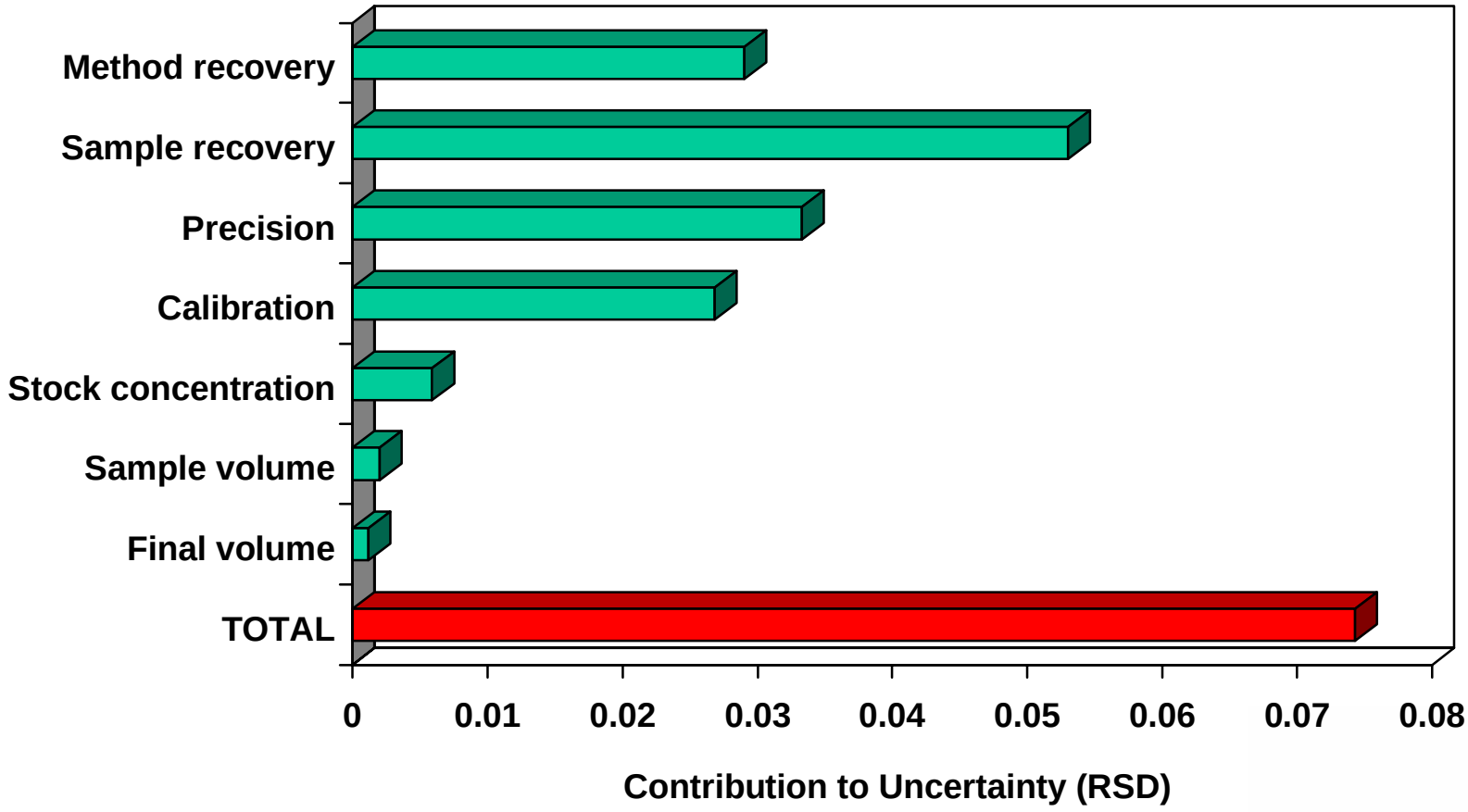
Uncertainty Components

Determination of Acesulfam-K



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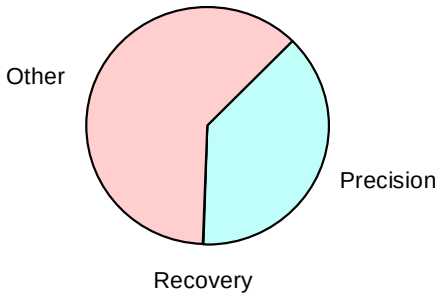
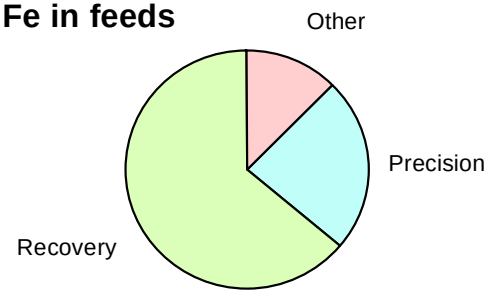
“Precision and Bias” contributions to uncertainty

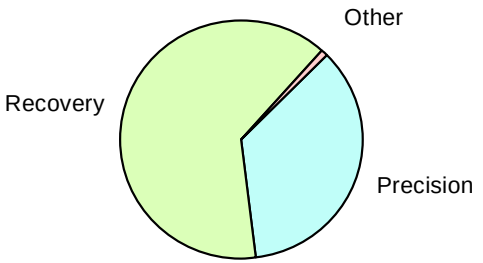
Crude Fibre (2.5%)



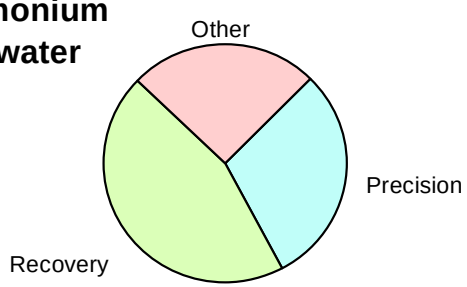
Fe in feeds



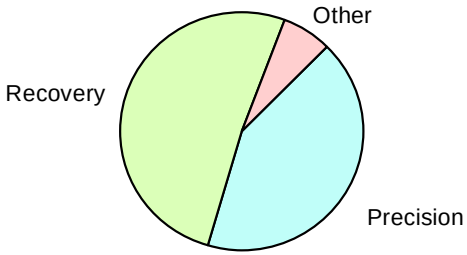
As in PVC



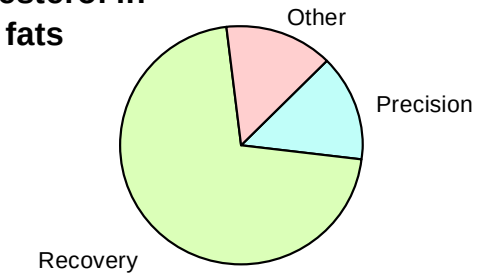
Ammonium in water



Hydroquinone in cosmetics



Cholesterol in fats



Precision

Bias uncertainty

Other

Conclusions

- Validation studies and measurement uncertainty studies are views of the same problem
  - "prediction and observation" = Science
- Where MU is required, analysts need methods of using validation data
  - EURACHEM/CITAC guide incorporates general guidance
  - Still some specific issues with detailed experimental studies

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