Bias in Clinical Chemistry

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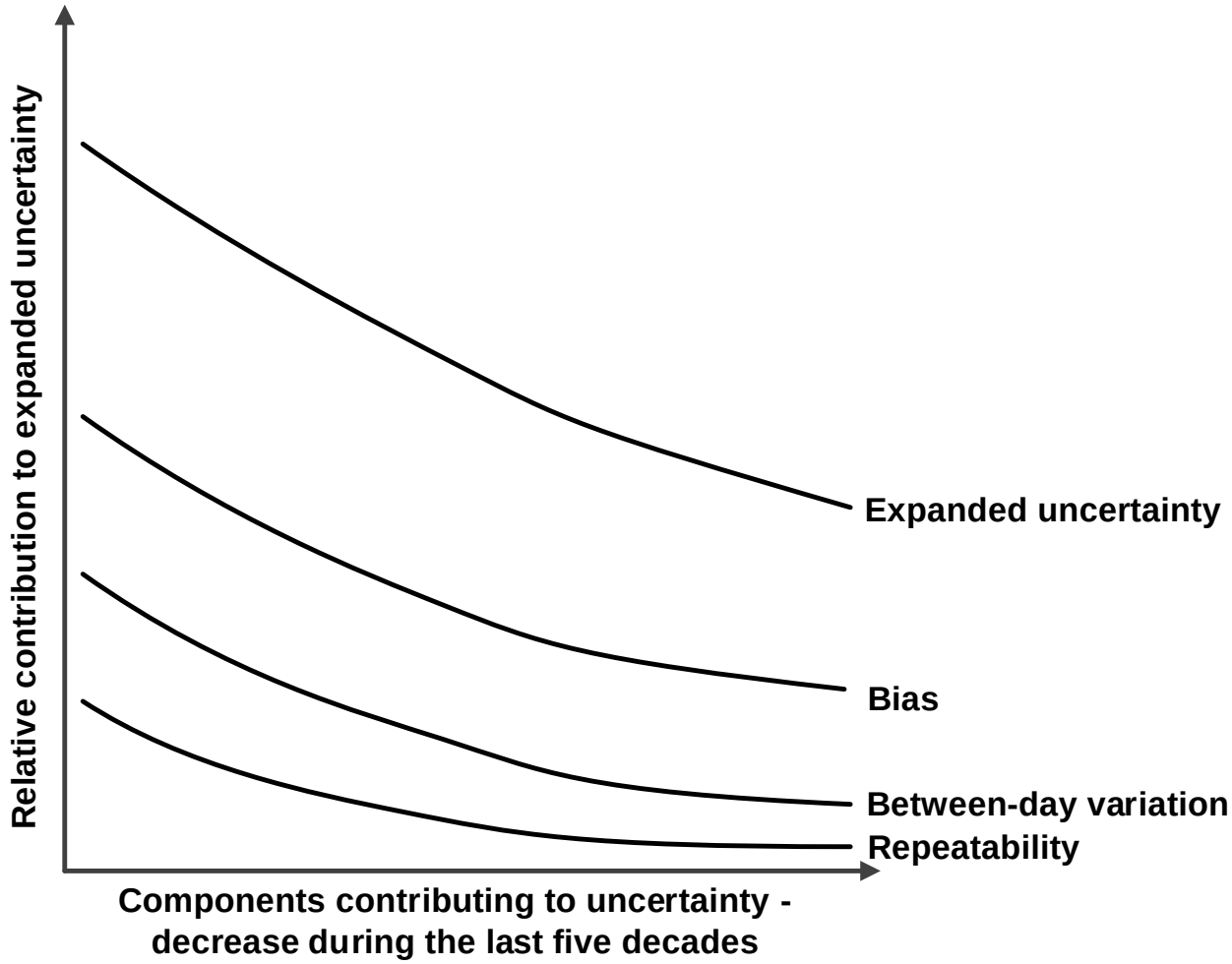
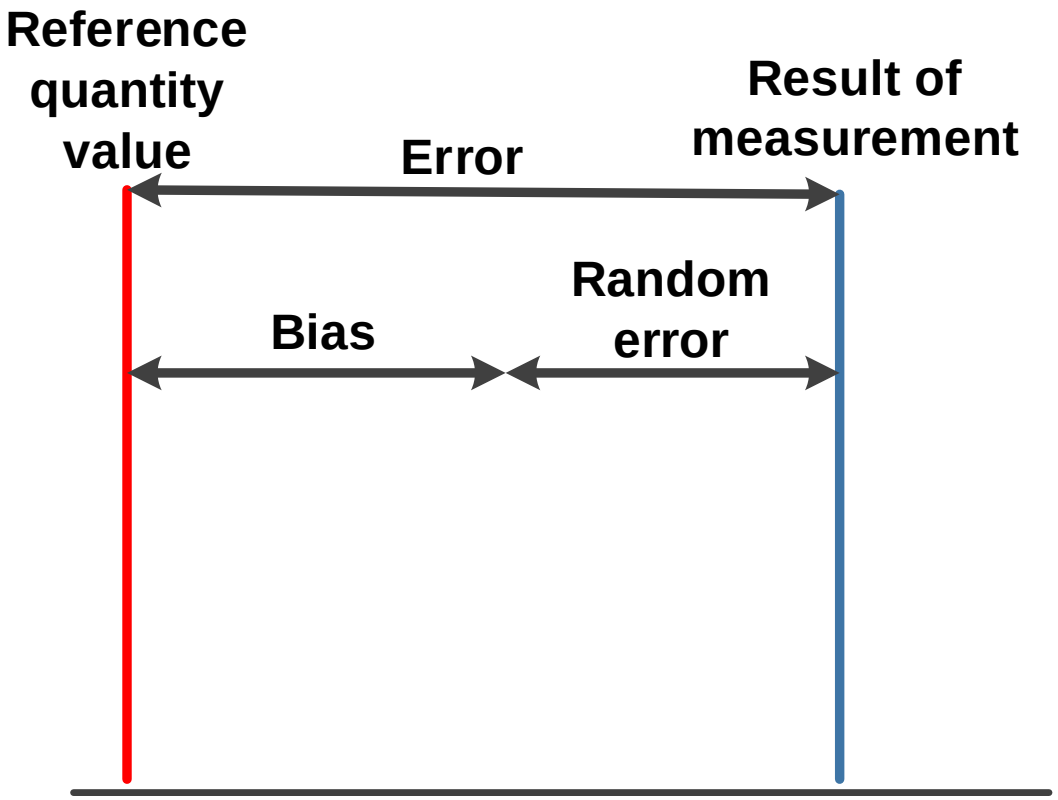
LINKÖPING UNIVERSITY

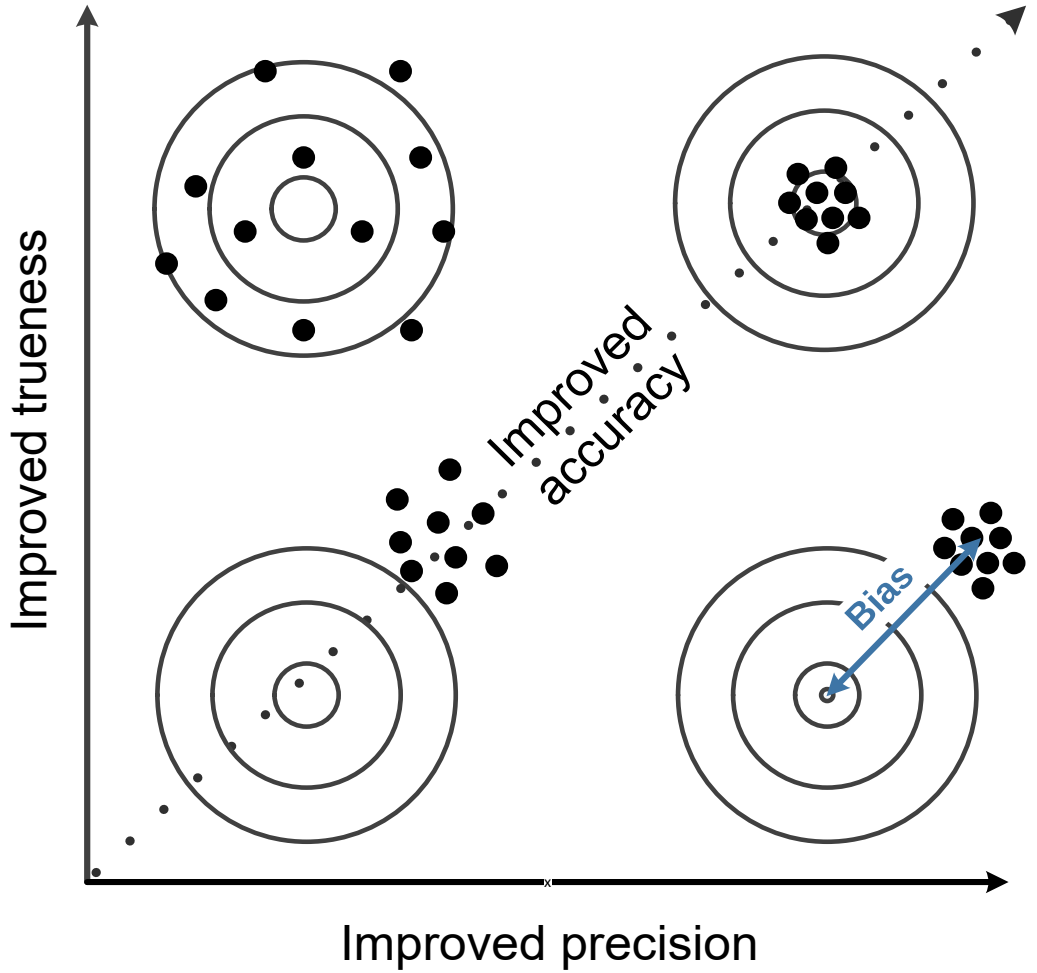
Bias – a major contribution to measurement uncertainty



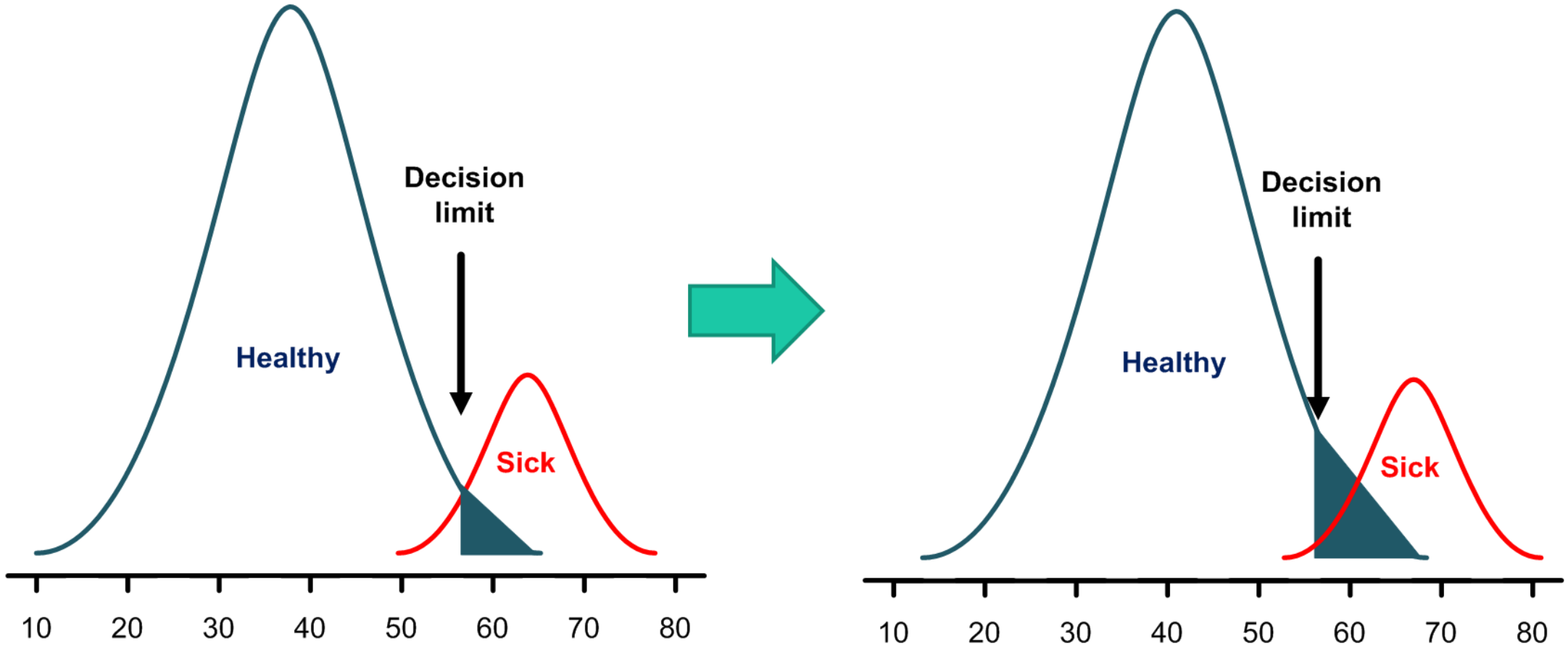
Error components - single measurement result



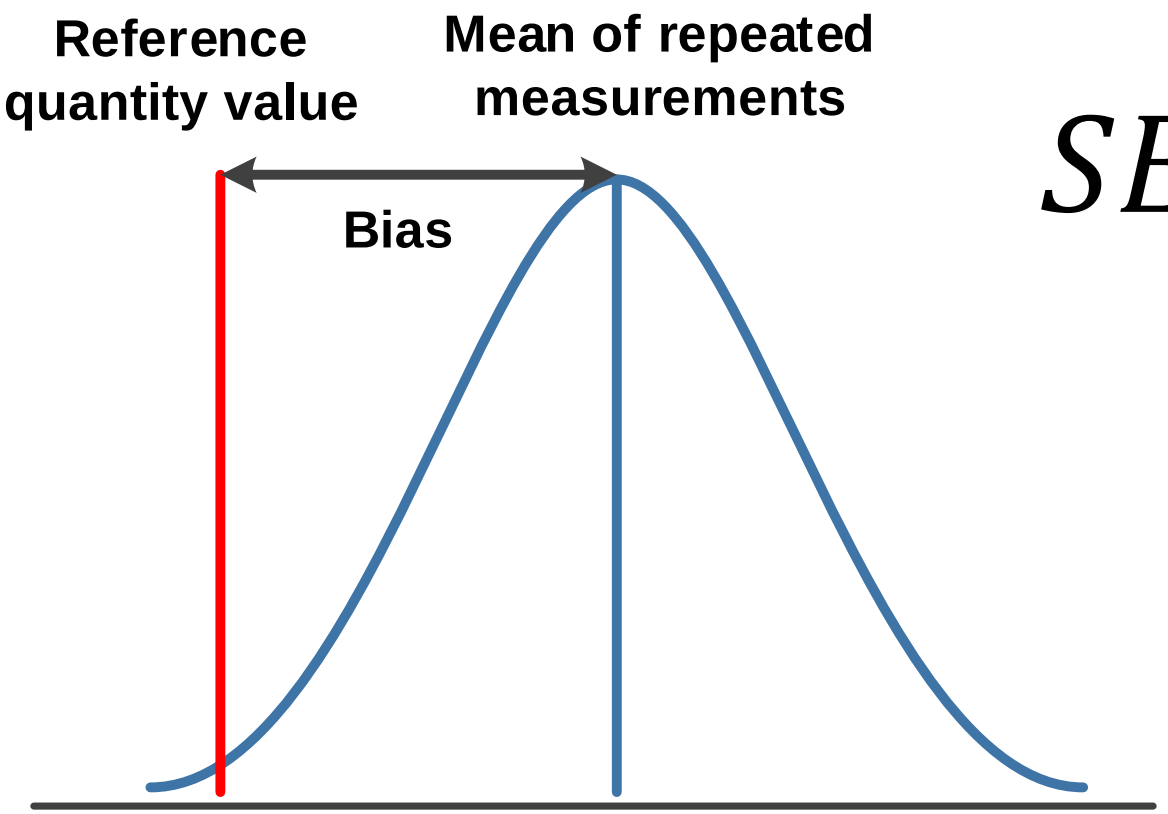
Bias and Imprecision



A bias of + 5 units means that healthy persons are diagnosed sick



Effect of repeated measurements

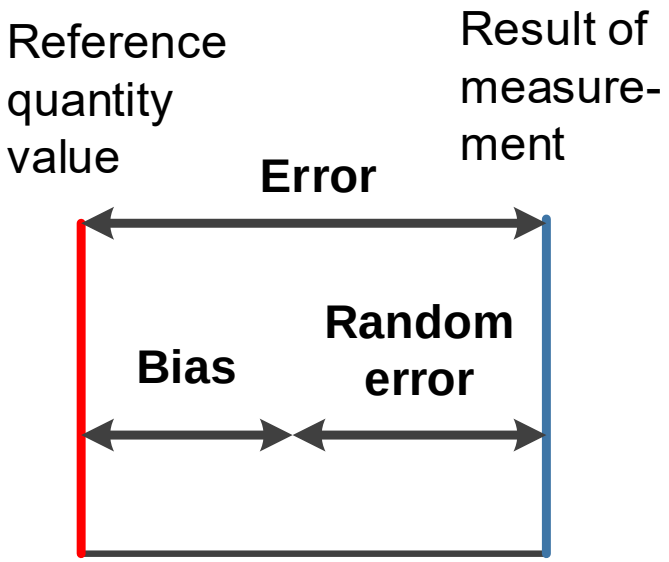


$$SEM = \frac{SD}{\sqrt{N}}$$

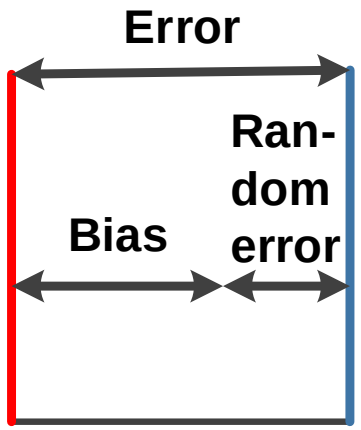
Effects of number of replicate measurements

The random error component of the uncertainty in determining the mean is inversely related to the square root of the number of observations – the standard error of the mean (SEM)

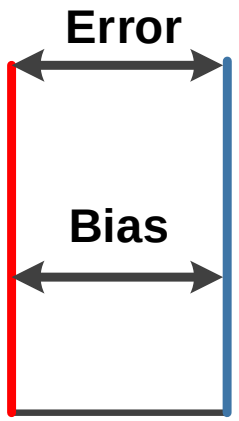
A
N=1



B
N=4



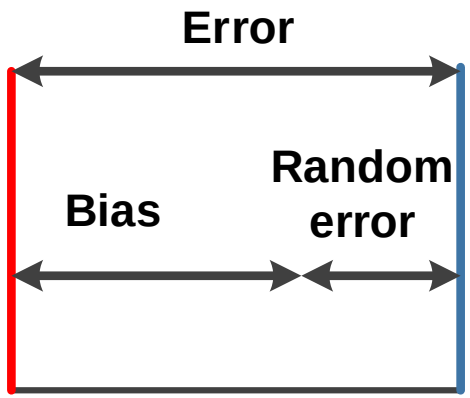
C
N=infinite



Effects of time

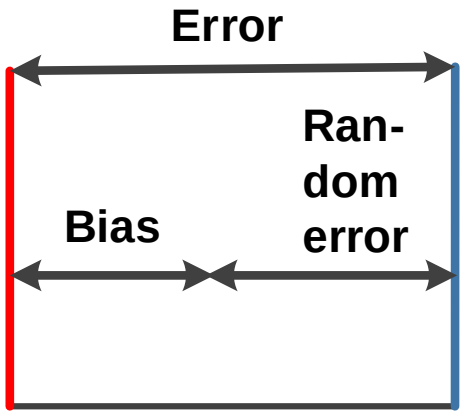
A

One day/One run



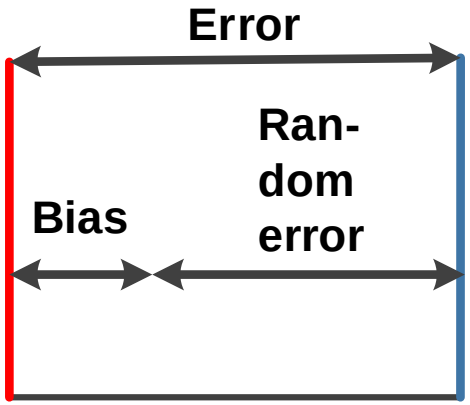
B

One week/Reagent lot/ Calibration

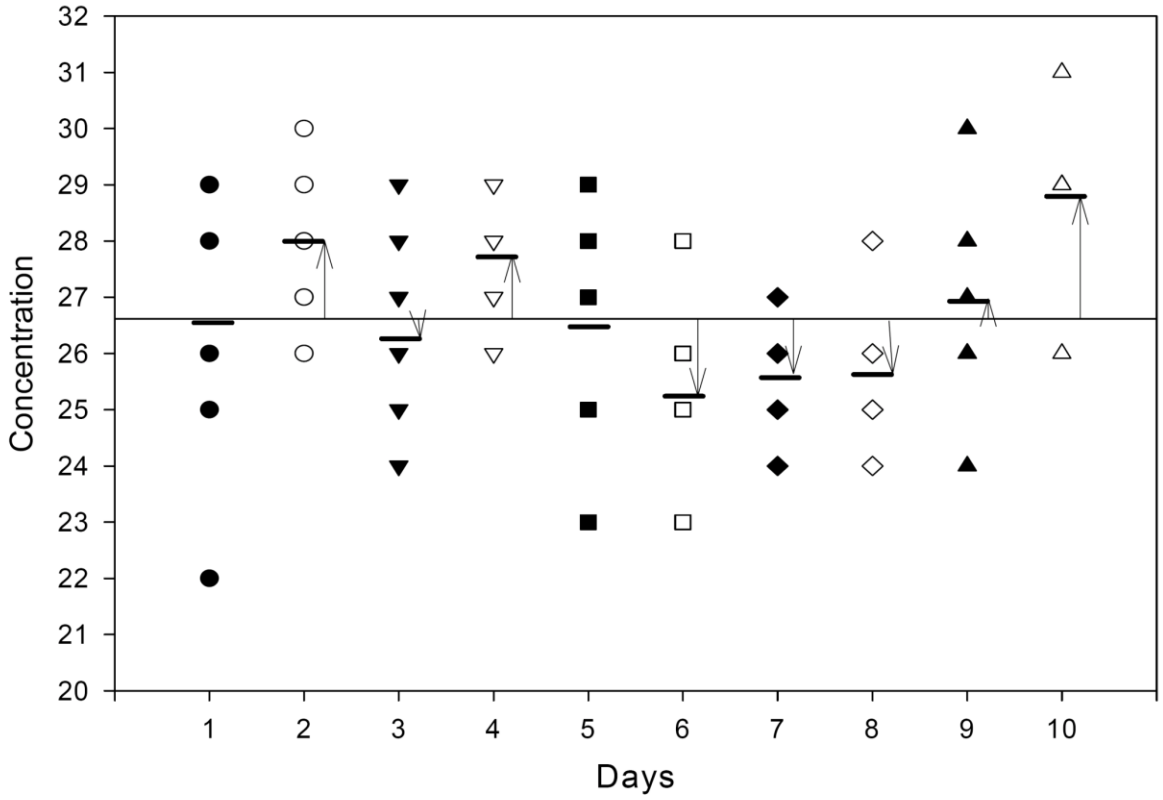


C

One year



Repeatability - reproducibility



Repeatability - reproducibility

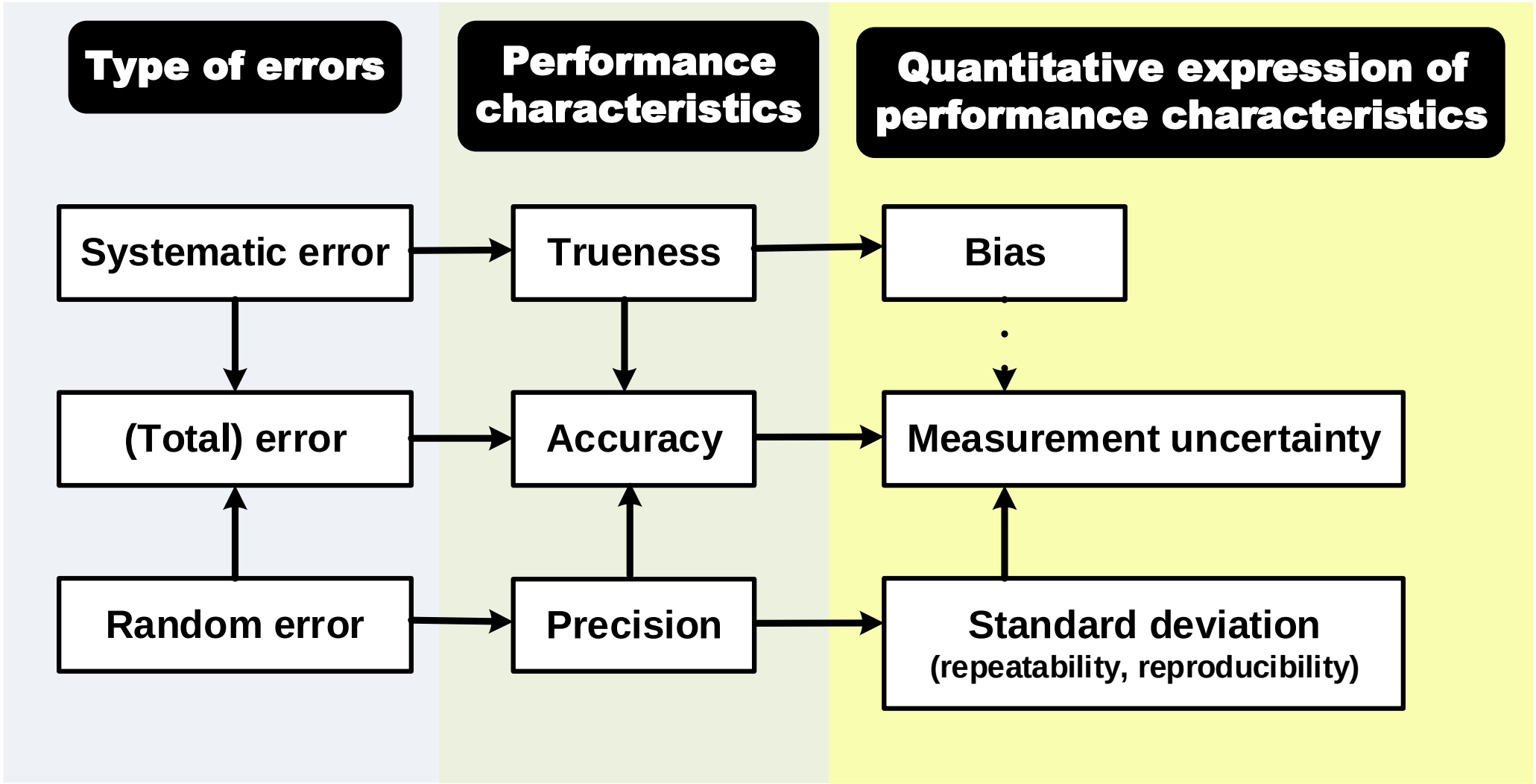
Repeatability

Intermediate reproducibility

Reproducibility

Condition of measurement, out of a set of conditions that includes the same measurement procedure, same operators, same measuring system, same operating conditions and same location, and replicate measurements on the same or similar objects over a short period of time

Condition of measurement, out of a set of conditions that includes different locations, operators, measuring systems, and replicate measurements on the same or similar objects


Type of errors
Performance characteristics
Quantitative expression of performance characteristics
Systematic error
Trueness
Bias
(Total) error
Accuracy
Measurement uncertainty
Random error
Precision
Standard deviation
(repeatability, reproducibility)

Handling bias

- **Eliminate** the bias
  - On the national and international level
  - On the local laboratory level
- **Include** the effects of bias in uncertainty calculations

Eliminating bias on the national and international level

1. Standardisation
2. Harmonization

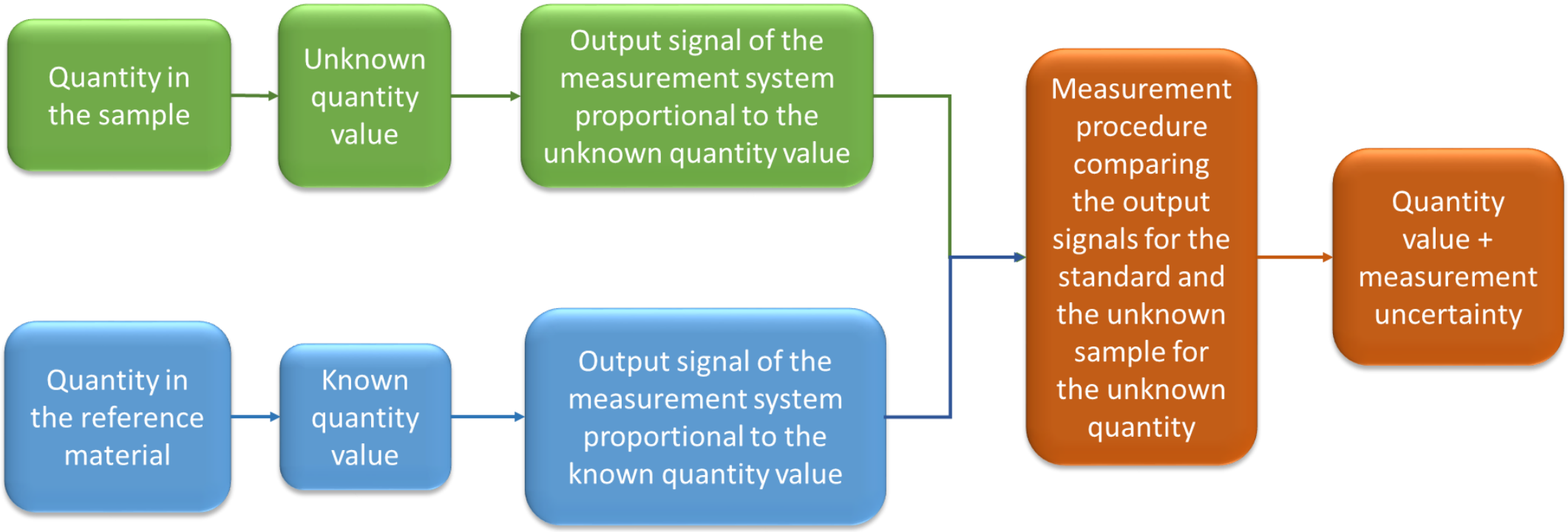
The measurand

- The *measurand* – “the quantity intended to be measured” is the quantity reflecting the concentration of the chemical constituent you intend to measure in the medically relevant “system” in the patient, e.g. in plasma as a reflection the effects of disease or treatment.
- Is our *intention* to measure the concentration of e. g. glucose in the plasma of the patient or in the patient plasma present in the tube presented to the measurement system?

The quantity

- *Quantity* is a generic concept describing the phenomenon (physical signal) being measured. The quantity is not the measurand but its value reflects the concentrations of the measurand.
- A quantity measured in chemistry depends on the chemical structures and chemical reactions that determine its value, but it is ultimately measured by *physical methods*. These physical methods which interact with atoms and molecules measure *quantity values* which visualise and quantify molecular structures or reactions that otherwise would remain invisible.

Measuring means comparing



Measurand – quantity inteded to be measured

Output signal - quantity subject to measurement

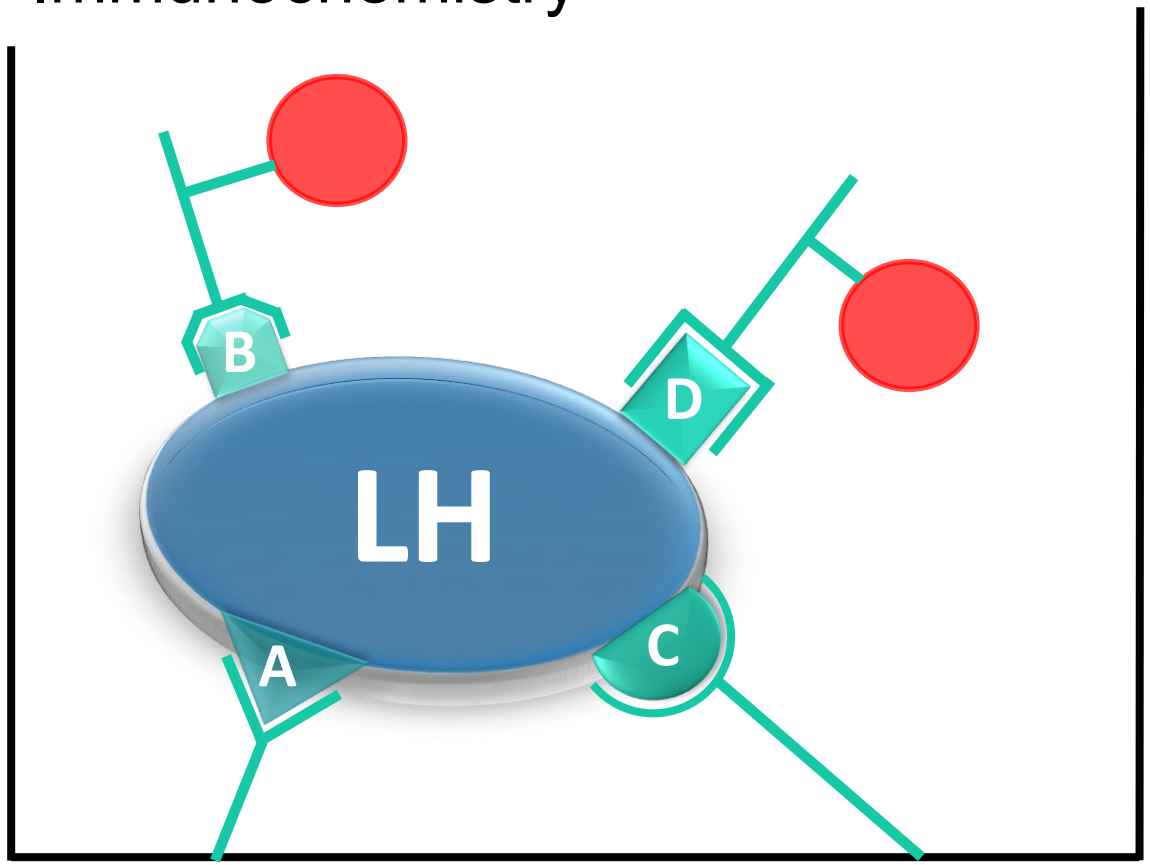
Ratio measurement

Measurement result

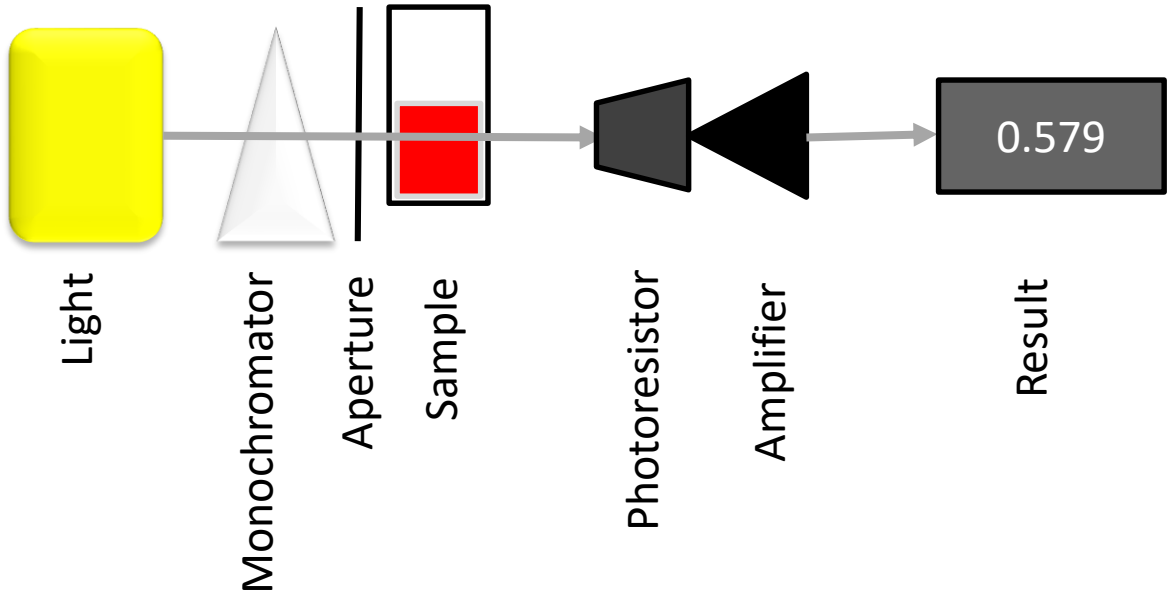
Comparing in chemistry

- Based on physical properties
- Prone to “influence quantities”

Immunochemistry

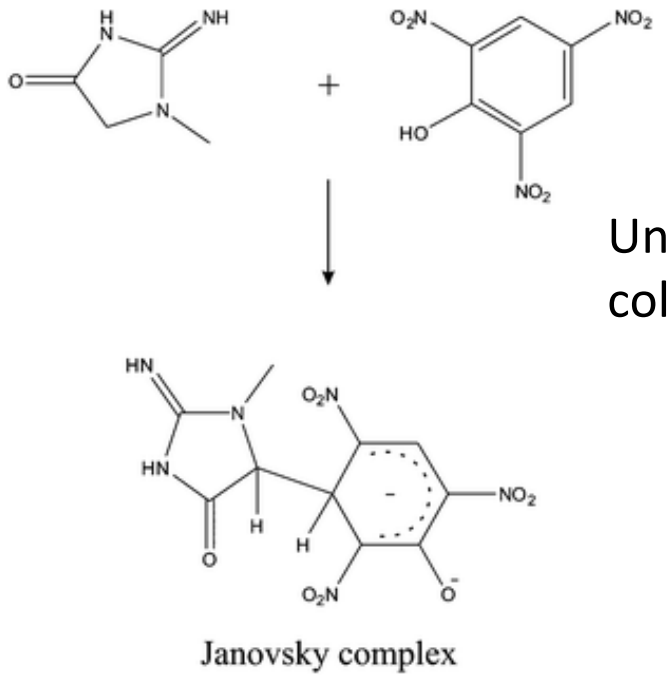


Photometry

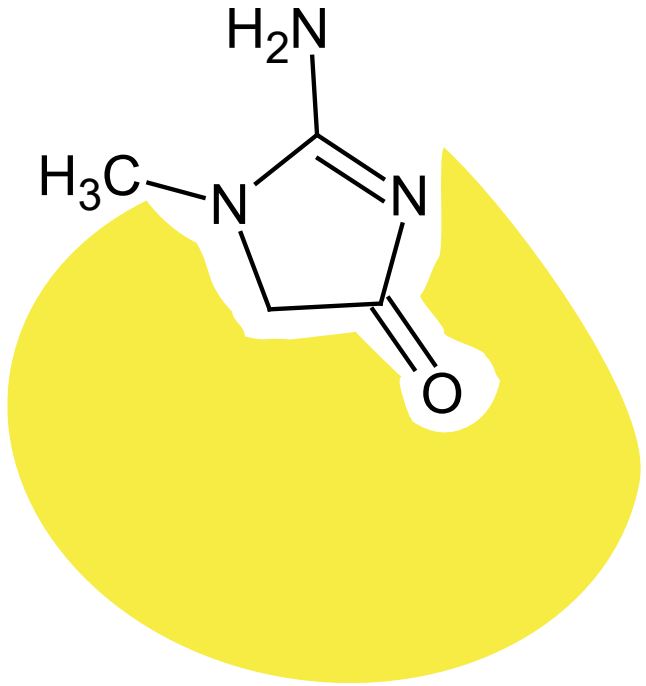


Selectivity VIM 3 - 4.13

”Property of a measuring system used with a measurement procedure, whereby it provides measured quantity value for one or more such that the values of each measurand are independent of other measurands or other quantities in the phenomenon, body, or substance being investigated.”



Unselective color reaction

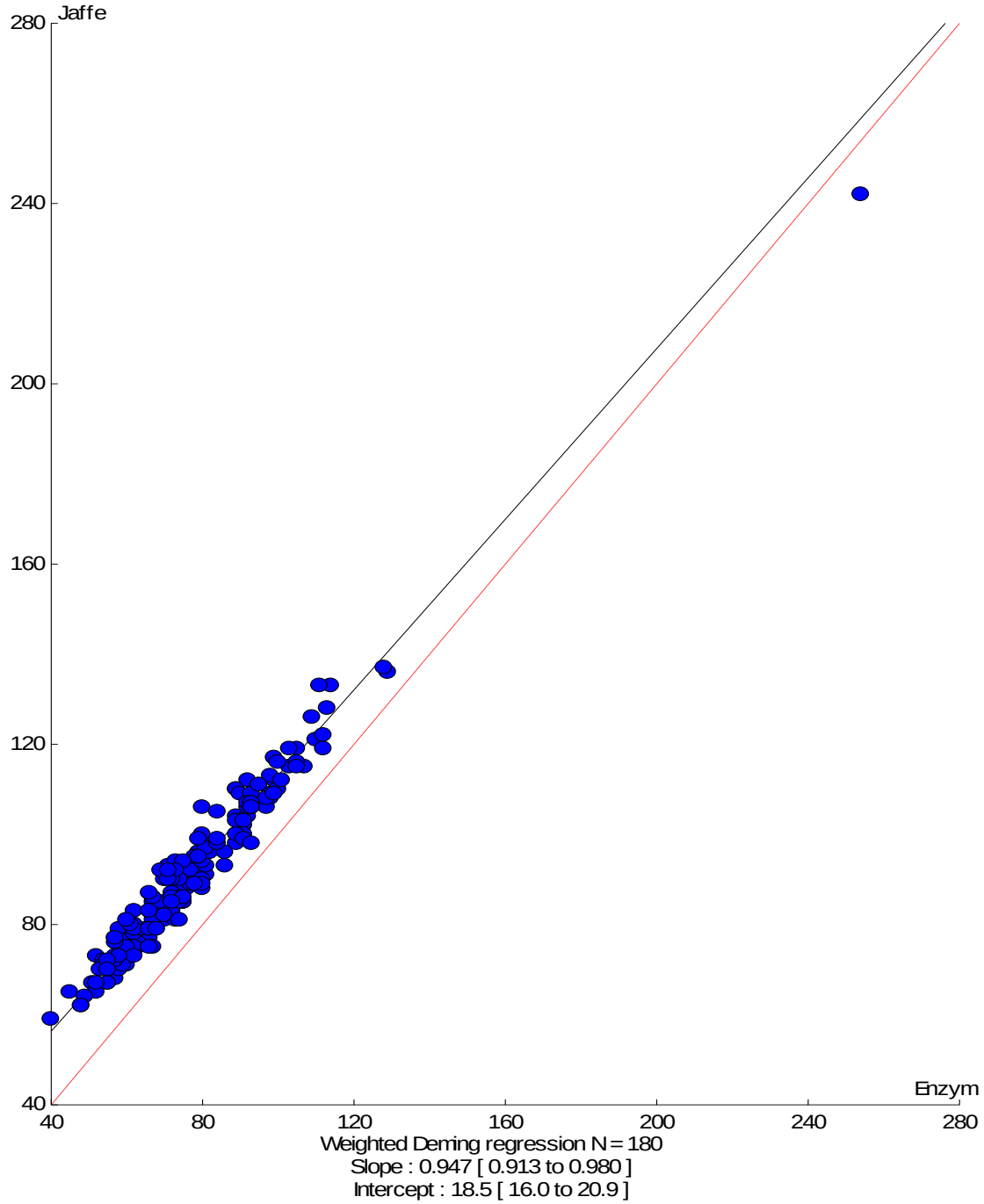


Selective enzymatic reaction

Comparison of the concentration of creatinine in 180 plasma samples measured using Jaffe and enzymatic methods

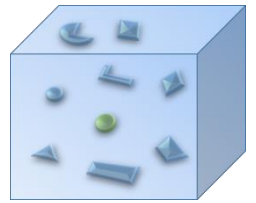
Jaffe = 0.947 * Enzymatic + 18.5

Enzymatic = Jaffe/0.947 – 18.5

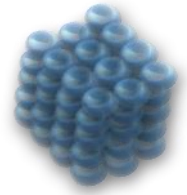


Influence quantities 1(2)

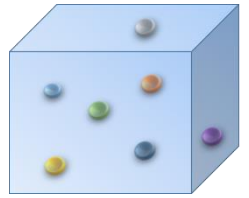
- The presence of “matrix factors”



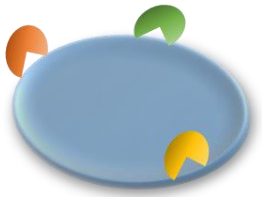
- Inability to produce the substance in a pure form that can be weighed



- Molecular heterogeneity, e.g. transferrin, LH, FSH, TSH



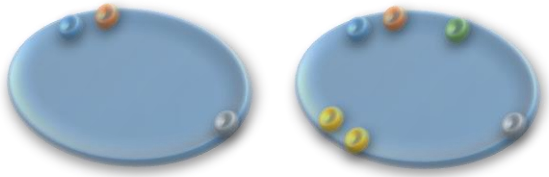
- Detection of different epitopes



Influence quantities 2(2)

- Lack of knowledge of which epitopes of molecules are medically most relevant, e.g. most substantial biological activity or best diagnostic properties

- Changes in posttranslational modification of molecules e.g. LH and FSH during the ovarial cycle



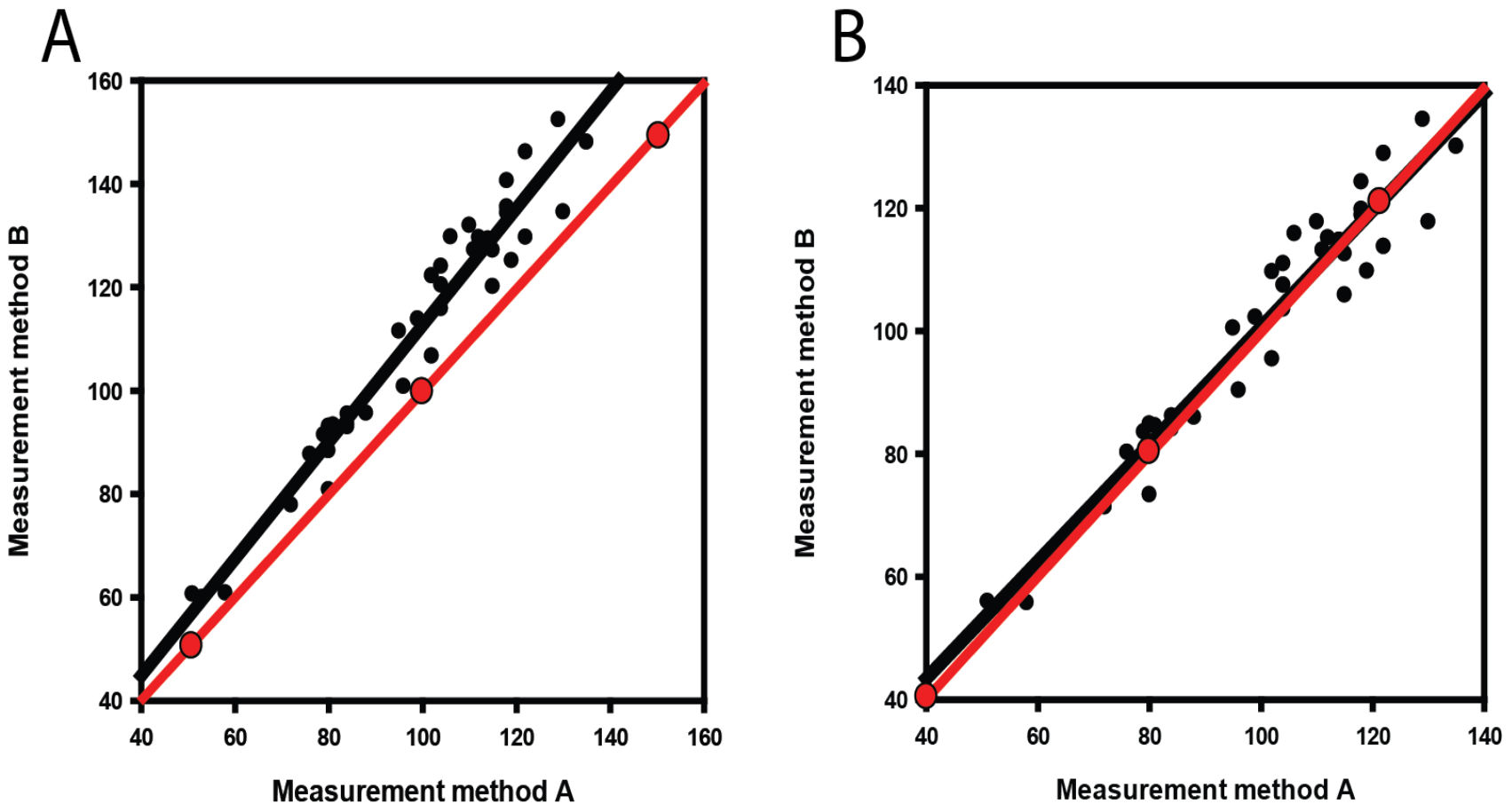
Matrix effects

- The combined effect of all components of the sample other than the analyte on the measurement of the measurand.
- If a specific component can be identified as causing a matrix effect then this is referred to as *interference*.

Commutability

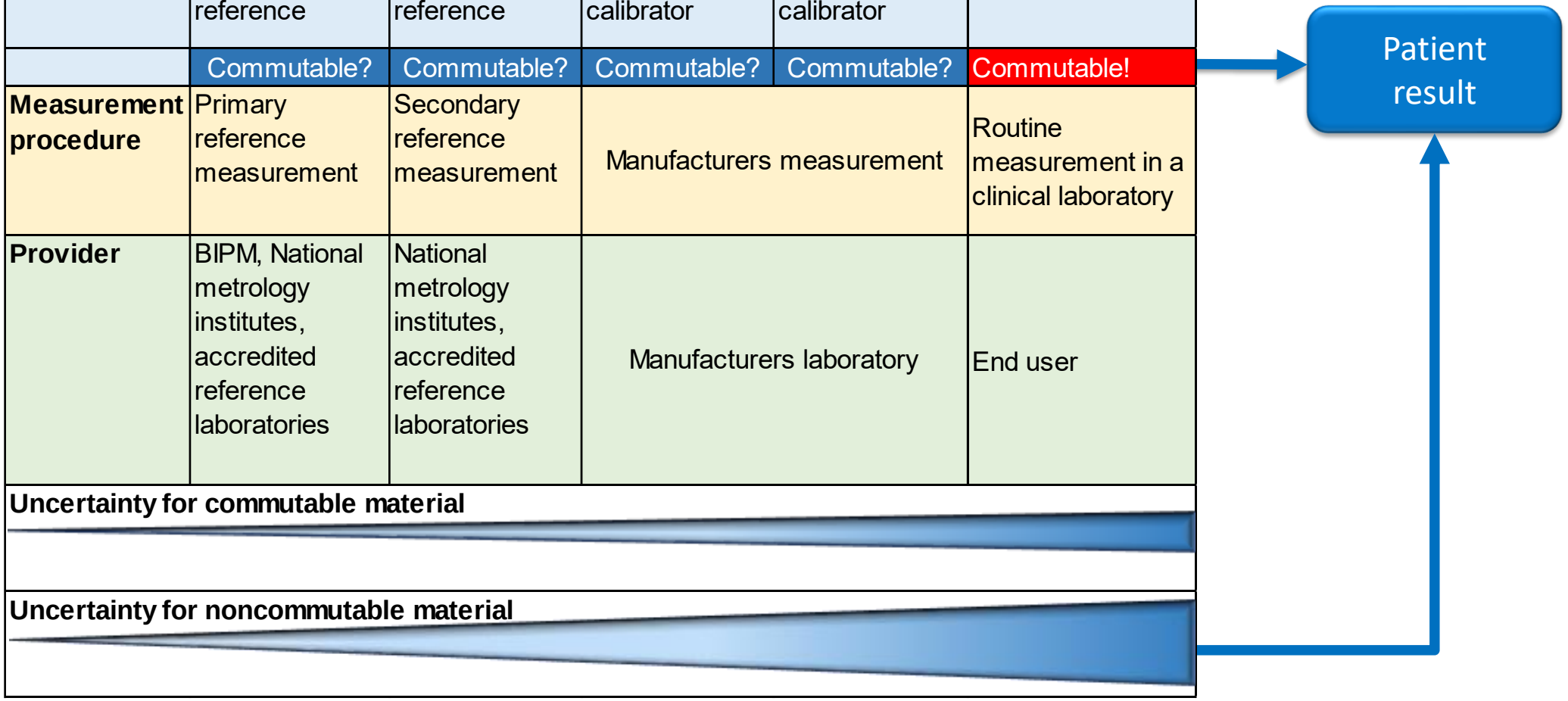
- To what extent reference materials, calibrators and control materials show matrix properties similar to those of fresh natural samples.
- Fresh natural patient samples represent the ultimately commutable materials for comparing measurement methods in clinical/biological chemistry.

Commutability



Commutability of the materials

Material	Primary reference	Secondary reference	Working calibrator	Product calibrator	Patient sample
	Commutable?	Commutable?	Commutable?	Commutable?	Commutable!
Measurement procedure	Primary reference measurement	Secondary reference measurement	Manufacturers measurement		Routine measurement in a clinical laboratory
Provider	BIPM, National metrology institutes, accredited reference laboratories	National metrology institutes, accredited reference laboratories	Manufacturers laboratory		End user
Uncertainty for commutable material					
Uncertainty for noncommutable material					



Traceability categories (ISO 17511)

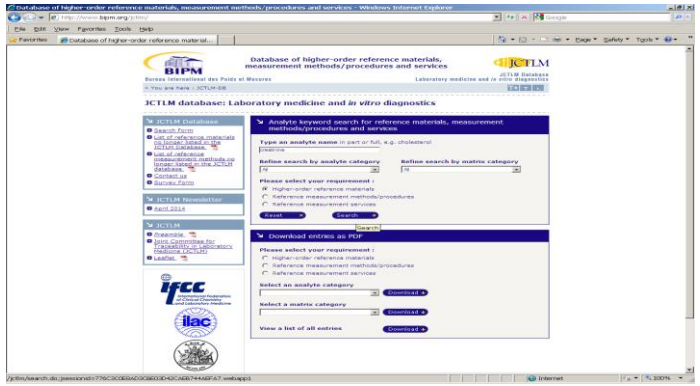
	Cate-gory	Reference measure-ment procedure	Primary (pure substance) reference material	Secondary (value assigned) reference material	Examples
Standardization	1	YES	YES	POSSIBLE	Electrolytes, glucose, cortisol
	2	YES	NO	POSSIBLE	Enzymes
	3	YES	NO	NO	Hemostatic factors
Harmonization	4	NO	NO	YES	Proteins, TSH, FSH, LH, tumor markers, HIV
	5	NO	NO	NO	Proteins, EBV, VZV

Reference materials

Reference material	Usage
Primary Reference Standard	Certified Standard with the highest metrological order. A calibrator with certified purity traceable to the SI unit with associated uncertainty.
Primary Reference Material	Material used for verification of a primary reference method, traceable to the primary reference standard. This material may also be used for verification of a routine method if shown to be commutable.
Secondary Reference Material	Material used for verification of a secondary reference method, traceable to the primary reference standard. This material may also be used for verification of a routine method if shown to be commutable.

Sources of Certified Reference Material and Methods

- JCTLM database (http://www.bipm.org/jctlm/)
  - Reference Materials
  - Reference Measurement Methods
  - Reference Measurement Services



Success stories in standardization in laboratory medicine

- Molecules with simple molecular structures, LC/GC MS, ion-selective electrodes
- Standardization of methods for measuring enzymatic activity
- Enzymatic methods for measuring substances earlier measured by non-specific colorimetric procedures (e.g. creatinine)
- Cholesterol
- Glycated hemoglobin
- Carbohydrate-deficient transferrin

Harmonization

- Equivalence of measurement results among different routine measurement procedures over time and space according to defined analytical and clinical performance goals
- Any process that enables the establishment of equivalence of reported values produced by different measurement procedures for the same measurand

Standardization and harmonization

- Harmonization encompasses standardization and also addresses those tests that can’t be calibrated by traceability to a reference measurement procedure
- Standardization is preferable to harmonization, but it is not always an option even when an internationally accepted calibrator is available. It is preferable due to its traceability to primary reference materials and primary reference measurement procedures

Harmonization has a broader scope than standardization

- Quality systems, e.g. ISO standards
- Concepts, terms, unit of measurement and coding systems
- Preanalytical procedures
  - Patient preparation
  - Specimen collection and handling
- Harmonizing measurement results
- Interpretation of results in medical contexts
- Reference intervals

Comparability and interchangeability of medical laboratory results

- Medical laboratory results should be comparable in time and space across the globe enabling unequivocal diagnosis and monitoring of treatment results
- Multitude of guidelines, standards (ISO), directives (EU IVD directive) and authorities (FDA) govern measurement systems and practices in medical laboratories. These are unfortunately only partially harmonized or unequivocal
  - The EU IVD directive e.g. does not clarify which reference measurement system should be used to fulfil its requirements
  - Organizations at the pinnacle of metrology, lack legal authority

Harmonization strategies 1(2) (Greenberg)

Attribute	Method 1	Method 2
Scheme	Hierarchical standardization per **ISO17511:2003**. **Top down** approach passing 'trueness' to lower order measurement procedures and calibrators.	Inter-method comparison as described by International Consortium for Harmonization of Clinical Laboratory Results (ICHCLR) (www.harmonization.net). **Bottom up** approach among routine (commercial) measurement procedures, with no SI traceability.
Reference measurement procedures	One or more **higher order reference measurement procedures available**, preferably fulfilling requirements of ISO 15193:2009	None available.
Reference materials	Certified purified reference materials and/or **commutable secondary reference materials**.	No higher order reference materials available. Panel(s) of **commutable human samples** assigned consensus values through harmonization studies. Some International Conventional Calibrators may be available (e.g. WHO materials), but usually not commutable.

Harmonization strategies 2(2) (Greenberg)

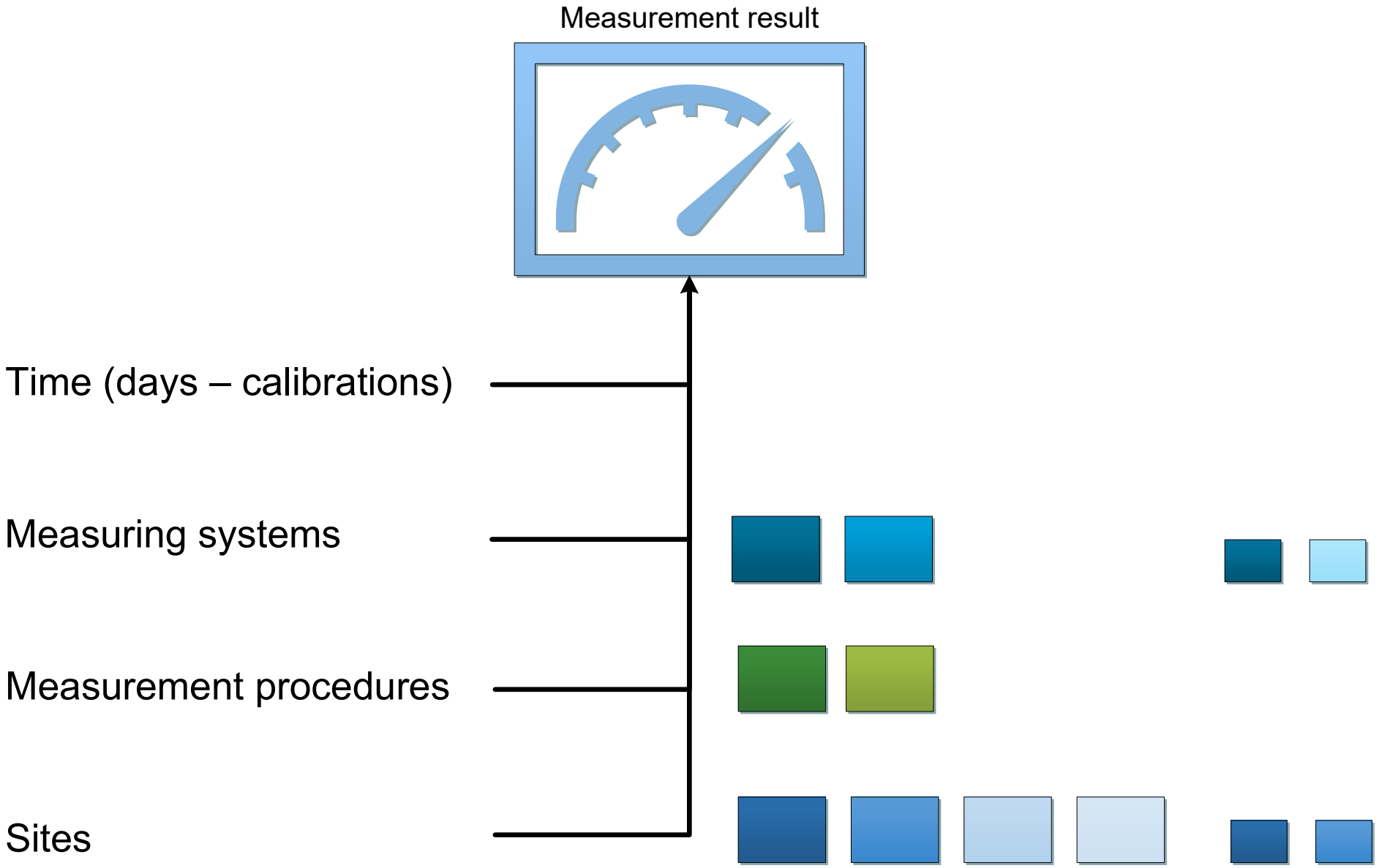
Attribute	Method 1	Method 2
Calibration traceability	Commercial calibrators and reported results for routine measurement procedures traceable to SI unit via a metrological reference system.	Commercial calibrators and reported results of routine measurement procedures not traceable to SI. **Traceability linked via inter-method comparison studies** of available commercial measurement procedures coupled with **mathematical recalibration** for removal of systematic differences among reported values.
Sustainability	**Inbuilt sustainability** through hierarchy of well-characterized and reproducible higher order and lower order reference measurement procedures and reference materials	**Risk for non-sustainability** of harmonized calibrations over time as routine methods and commercial calibrator lots change. Panels of patient samples used as “calibrators” in harmonization studies to be renewed over time (consumption and/or stability concerns.) Second and subsequent patient sample panels with values traceable to initial sample panel; presumes well-defined specifications for panel member selection.

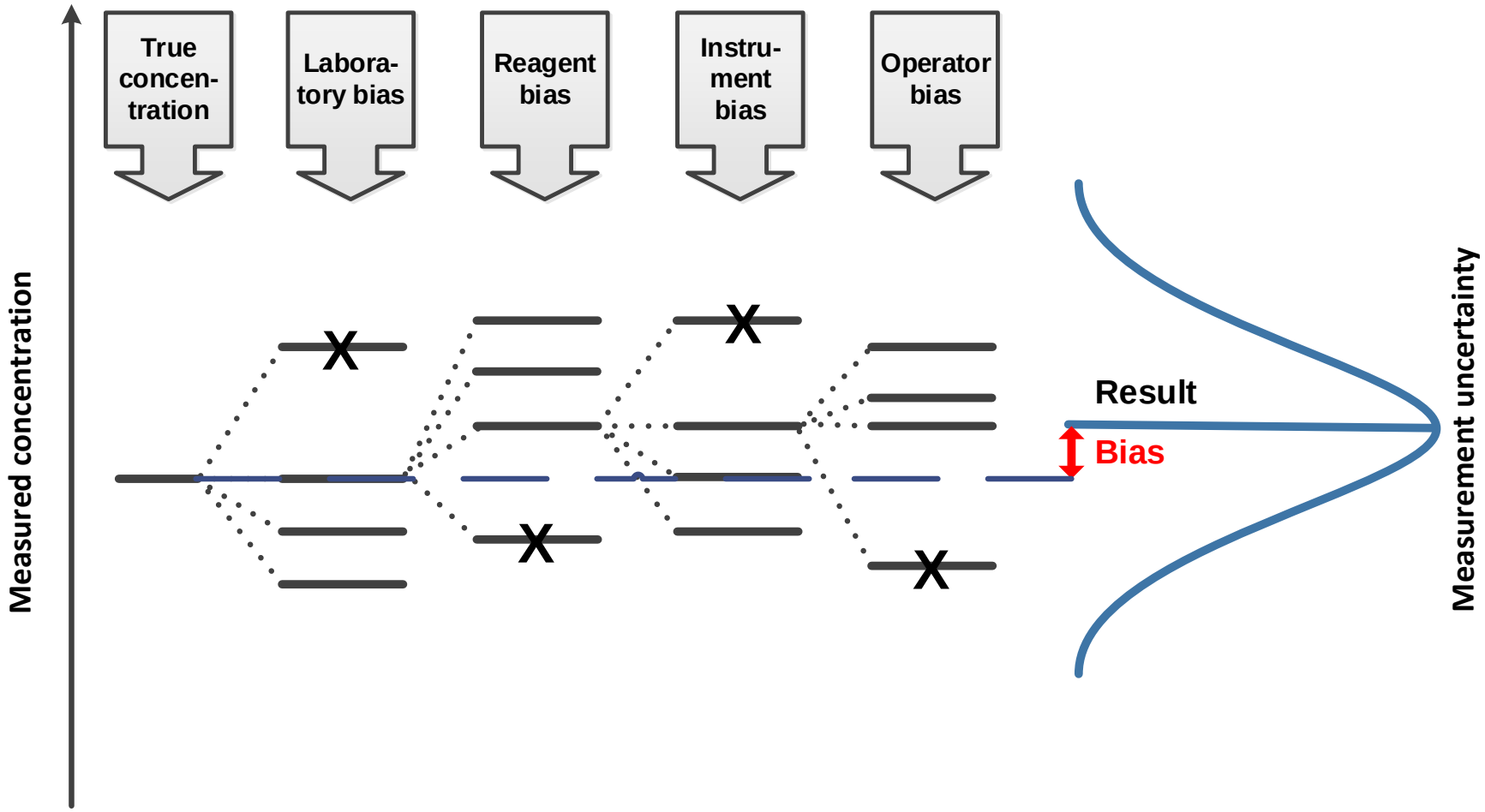
Eliminating bias on the local/laboratory level

1. Make sure that there is a shared responsibility for the quality of each measurand in the entire laboratory
2. Use the same stabilised control material throughout the entire laboratory
3. Use split-sample techniques
4. Establish a computer system where all control results are open for everybody within the laboratory to see
5. Minimize the number of different measuring procedures and measurement systems
6. Use bias and variance component analysis to identify the measurement systems in need of overhaul

County of Östergötland, Sweden

470 000 inhabitants
4 hospitals
36 primary health care centers

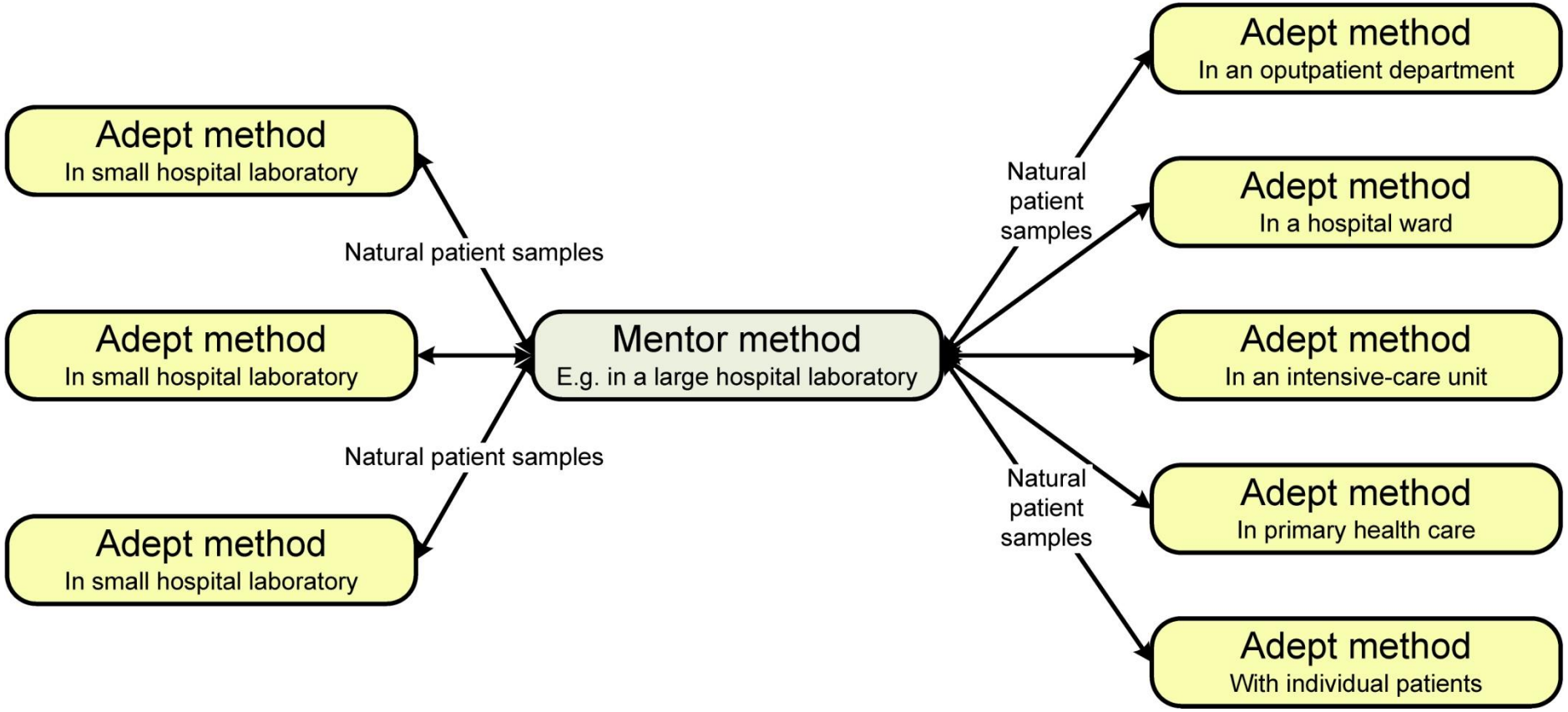

Measurement result
Time (days – calibrations)
Measuring systems
Measurement procedures
Sites


True concen-tration
Labora-tory bias
Reagent bias
Instru-ment bias
Operator bias
Measured concentration
Result
Bias
Measurement uncertainty

Split – sample techniques

1. Using the same logistic normally used for sending samples to the central laboratory
2. Computerize the logistics and evaluation of the data

Split sample/Mentor methods

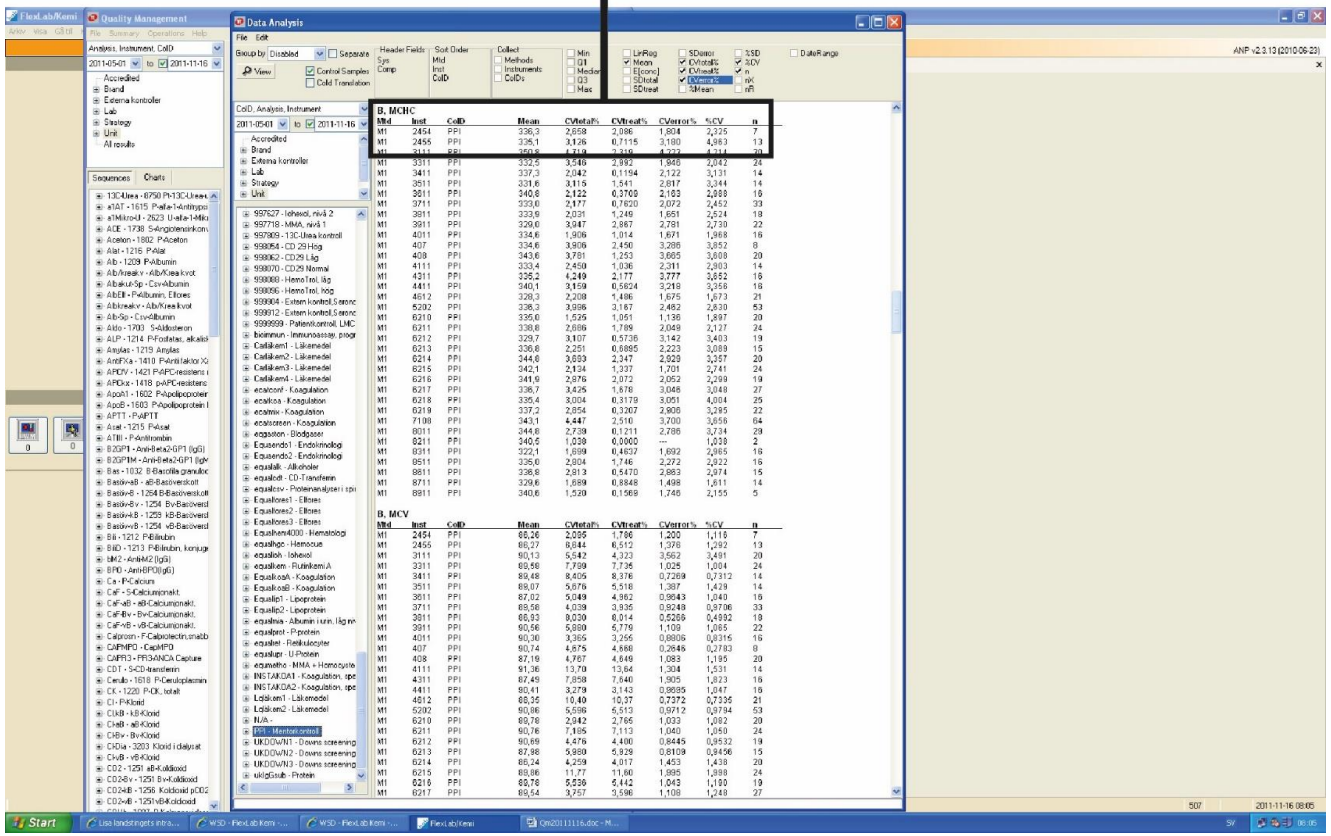


Norming results

$$\text{Normed result} = \frac{\text{Adept - Mentor}}{\text{Mentor}} * 100$$

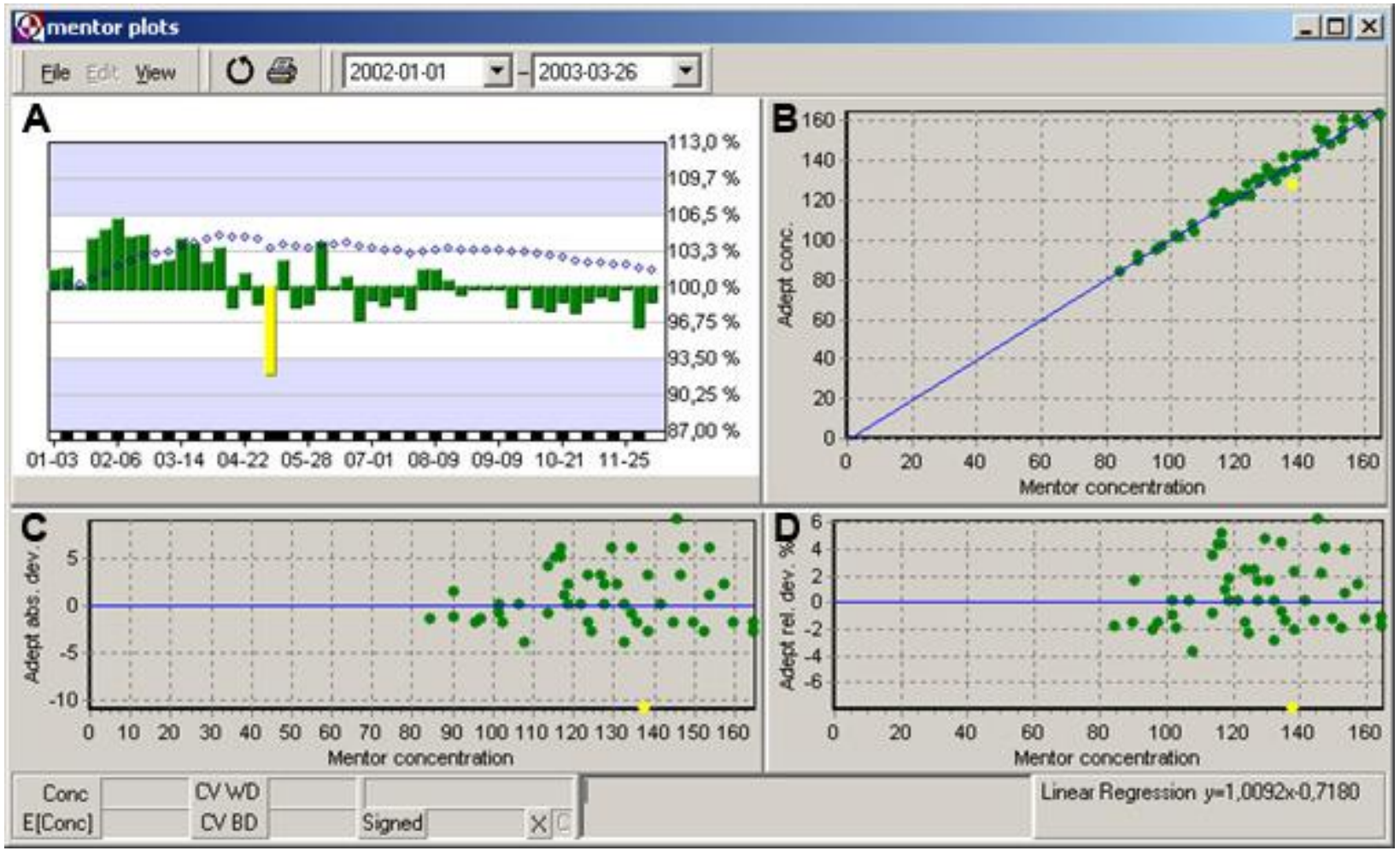
B, MCHC

Mtd	Inst	ColD	Mean	CVtotal%	CVtreat%	CVerror%	%CV	n
M1	2454	PPI	336,3	2,658	2,086	1,804	2,325	7
M1	2455	PPI	335,1	3,126	0,7115	3,180	4,963	13
M1	3111	PPI	350,8	4,719	2,319	4,222	4,214	20
M1	3311	PPI	332,5	3,546	2,992	1,946	2,042	24



Variance component analysis

Bias in measurement of endogenous substances



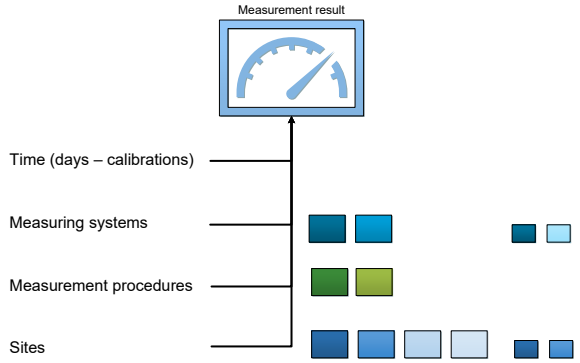
Advantages of split samples

1. The the material has optimal matrix properties (is commutable)
2. The material is available without cost for all laboratories accepting routine patient samples
3. There is general agreement that all measurement systems and reagents should optimally result in identical results when analyzing the same patient samples
4. The methods are optimal for identifying the measurement system(s) in the organization that contribute the largest part of the overall measurement uncertainty due to bias. Split sample methods are laborious in the absence of effective computerized systems, but convenient when properly implemented

Bias elimination at the laboratory level – practical laboratory work

Shared responsibility for the quality of each measurand in the entire laboratory

- A sample from a certain patient can encounter all factors causing variation of results in the laboratory
- The overall measurement uncertainty therefore needs to be an issue and shared responsibility for the entire organization
- In time this caters for a better working environment in the entire organization

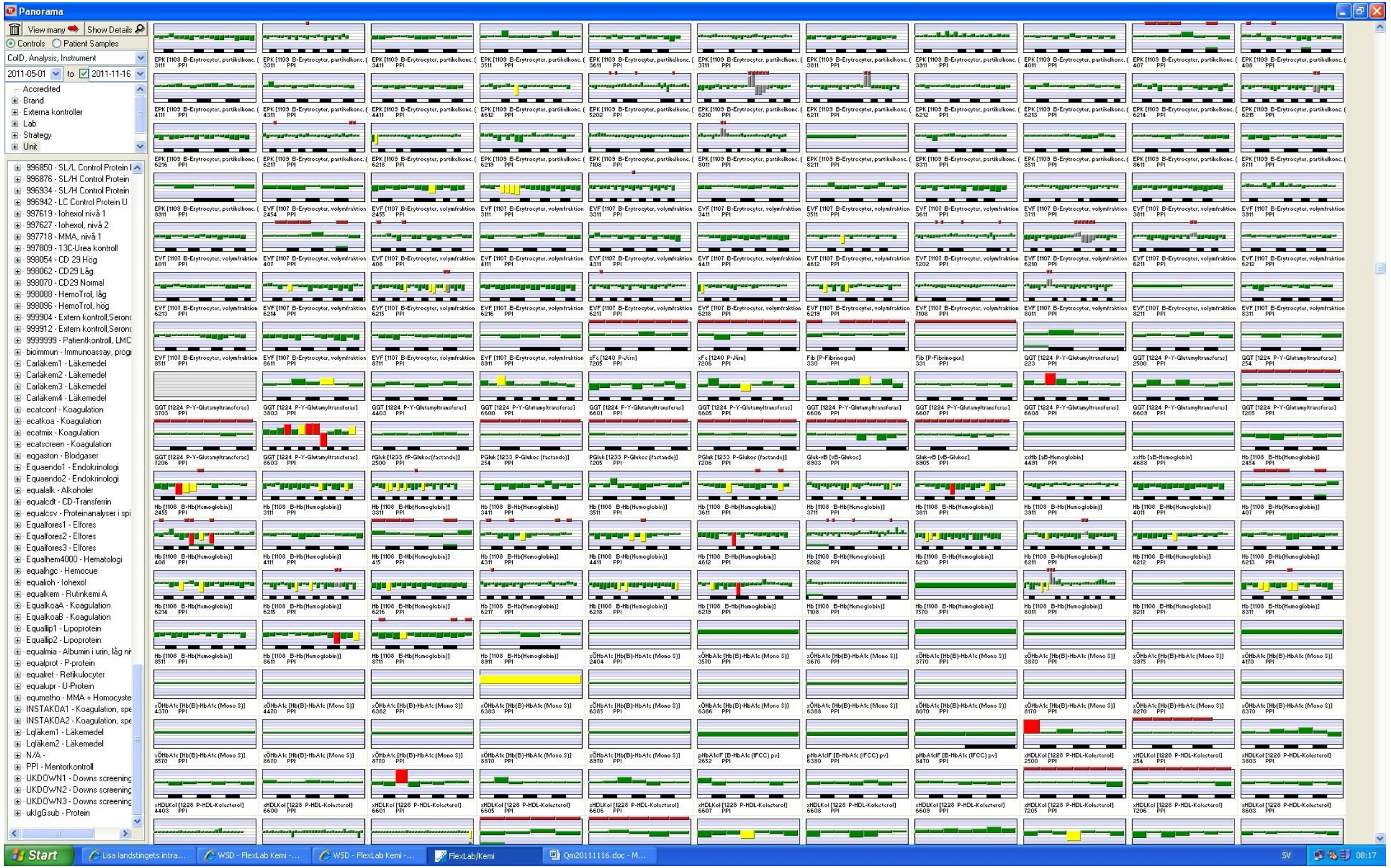


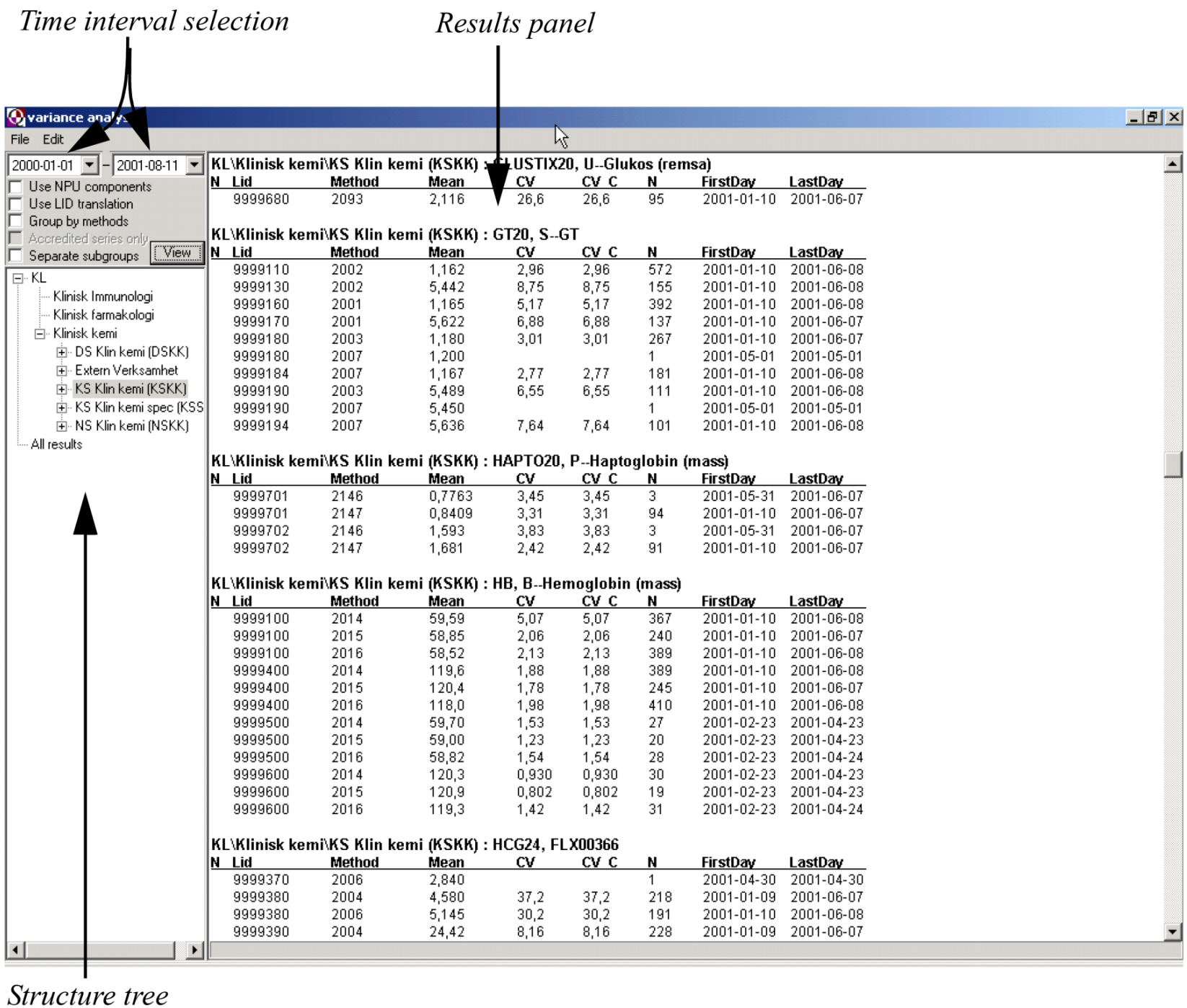
Use the same stabilised control material throughout the entire laboratory

1. Test materials from different producers for optimal matrix properties in the situation you have in your own laboratory
2. Materials of human plasma/serum origin are most likely to show optimal matrix properties
3. Purchase a supply of the control material lasting at least one year – preferably two years

Establish a computer system where all control results are open for everybody within the laboratory to see

- Appropriate computerized system is a prerequisite to be able to shoulder shared responsibility for the measurement uncertainty of each measurand in the laboratory
- Both graphical and statistical presentation


Panorama
View many
Show Details
Controls
Patient Samples
ColD, Analysis, Instrument
2011-05-01
to
2011-11-16
Accredited
Brand
Externa kontroller
Lab
Strategy
Unit
996850 - SL/L Control Protein I
996876 - SL/H Control Protein
996934 - SL/H Control Protein
996942 - LC Control Protein U
997619 - Iohexol nivå 1
997627 - Iohexol, nivå 2
997718 - MMA, nivå 1
997809 - 13C-Urea kontroll
998054 - CD 29 Hög
998062 - CD29 Låg
998070 - CD29 Normal
998088 - HemoTrol, låg
998096 - HemoTrol, hög
999904 - Extern kontroll,Seronc
999912 - Extern kontroll,Seronc
9999999 - Patientkontroll, LMC
bioimmun - Immunoassay, progi
Carläkem1 - Läkemedel
Carläkem2 - Läkemedel
Carläkem3 - Läkemedel
Carläkem4 - Läkemedel
ecatconf - Koagulation
ecatkoa - Koagulation
ecatmix - Koagulation
ecatscreen - Koagulation
eqgaston - Blodgaser
Equaendo1 - Endokrinologi
Equaendo2 - Endokrinologi
equalalk - Alkoholer
equalcdt - CD-Transferrin
equalcsv - Proteinanalyser i spi
Equalfores1 - Elfores
Equalfores2 - Elfores
Equalfores3 - Elfores
Equalhem4000 - Hematologi
equalhgc - Hemocue
equalioh - Iohexol
equalkem - Rutinkemi A
EqualkoaA - Koagulation
EqualkoaB - Koagulation
Equallip1 - Lipoprotein
Equallip2 - Lipoprotein
equalmia - Albumin i urin, låg nir
equalprot - P-protein
equalret - Retikulocyter
equalupr - U-Protein
equmetho - MMA + Homocyste
INSTAKOA1 - Koagulation, spe
INSTAKOA2 - Koagulation, spe
Lqläkem1 - Läkemedel
Lqläkem2 - Läkemedel
N/A -
PPI - Mentorkontroll
UKDOWN1 - Downs screening
UKDOWN2 - Downs screening
UKDOWN3 - Downs screening
uklgGsub - Protein
Start
Lisa landstingets intra...
WSD - FlexLab Kemi -...
WSD - FlexLab Kemi -...
FlexLab/Kemi
Qm20111116.doc - M...
SV
08:17


Time interval selection
Results panel
variance anal
File Edit
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2001-08-11
Use NPU components
Use LID translation
Group by methods
Accredited series only
Separate subgroups
View
KL
Klinisk Immunologi
Klinisk farmakologi
Klinisk kemi
DS Klin kemi (DSKK)
Extern Verksamhet
KS Klin kemi (KSKK)
KS Klin kemi spec (KSS
NS Klin kemi (NSKK)
All results
KL\Klinisk kemi\KS Klin kemi (KSKK) : GLUSTIX20, U--Glukos (remsa)
N Lid Method Mean CV CV_C N FirstDay LastDay
9999680 2093 2,116 26,6 26,6 95 2001-01-10 2001-06-07
KL\Klinisk kemi\KS Klin kemi (KSKK) : GT20, S--GT
N Lid Method Mean CV CV_C N FirstDay LastDay
9999110 2002 1,162 2,96 2,96 572 2001-01-10 2001-06-08
9999130 2002 5,442 8,75 8,75 155 2001-01-10 2001-06-08
9999160 2001 1,165 5,17 5,17 392 2001-01-10 2001-06-08
9999170 2001 5,622 6,88 6,88 137 2001-01-10 2001-06-07
9999180 2003 1,180 3,01 3,01 267 2001-01-10 2001-06-07
9999180 2007 1,200 1 2001-05-01 2001-05-01
9999184 2007 1,167 2,77 2,77 181 2001-01-10 2001-06-08
9999190 2003 5,489 6,55 6,55 111 2001-01-10 2001-06-08
9999190 2007 5,450 1 2001-05-01 2001-05-01
9999194 2007 5,636 7,64 7,64 101 2001-01-10 2001-06-08
KL\Klinisk kemi\KS Klin kemi (KSKK) : HAPTO20, P--Haptoglobin (mass)
N Lid Method Mean CV CV_C N FirstDay LastDay
9999701 2146 0,7763 3,45 3,45 3 2001-05-31 2001-06-07
9999701 2147 0,8409 3,31 3,31 94 2001-01-10 2001-06-07
9999702 2146 1,593 3,83 3,83 3 2001-05-31 2001-06-07
9999702 2147 1,681 2,42 2,42 91 2001-01-10 2001-06-07
KL\Klinisk kemi\KS Klin kemi (KSKK) : HB, B--Hemoglobin (mass)
N Lid Method Mean CV CV_C N FirstDay LastDay
9999100 2014 59,59 5,07 5,07 367 2001-01-10 2001-06-08
9999100 2015 58,85 2,06 2,06 240 2001-01-10 2001-06-07
9999100 2016 58,52 2,13 2,13 389 2001-01-10 2001-06-08
9999400 2014 119,6 1,88 1,88 389 2001-01-10 2001-06-08
9999400 2015 120,4 1,78 1,78 245 2001-01-10 2001-06-07
9999400 2016 118,0 1,98 1,98 410 2001-01-10 2001-06-08
9999500 2014 59,70 1,53 1,53 27 2001-02-23 2001-04-23
9999500 2015 59,00 1,23 1,23 20 2001-02-23 2001-04-23
9999500 2016 58,82 1,54 1,54 28 2001-02-23 2001-04-24
9999600 2014 120,3 0,930 0,930 30 2001-02-23 2001-04-23
9999600 2015 120,9 0,802 0,802 19 2001-02-23 2001-04-23
9999600 2016 119,3 1,42 1,42 31 2001-02-23 2001-04-24
KL\Klinisk kemi\KS Klin kemi (KSKK) : HCG24, FLX00366
N Lid Method Mean CV CV_C N FirstDay LastDay
9999370 2006 2,840 1 2001-04-30 2001-04-30
9999380 2004 4,580 37,2 37,2 218 2001-01-09 2001-06-07
9999380 2006 5,145 30,2 30,2 191 2001-01-10 2001-06-08
9999390 2004 24,42 8,16 8,16 228 2001-01-09 2001-06-07
Structure tree

Minimize the number of different measuring procedures and measurement systems

- Must be done over an extended period of time for economic reasons
- Make lot-number variability amongst the important criteria when selecting a supplier

Change LOT-numbers simultaneously throughout the entire laboratory

- Purchase large amounts of the same LOT-numbers in order to minimize the number of LOT-number changes/recalibrations
- Receive reagents centrally and use your distribution network to distribute reagents, calibrators and controls

“If it ain't broke, don't fix it”

- Frequent lot-number changes/recalibrations are a common cause of uncertainty
- Identify the most important sources of variation and eliminate them

Use bias- and variance component analysis to identify the measurement systems in need of overhaul

- Create automated computer solutions for the purpose
- Simple solutions including MS Excel spreadsheets will in time prove insufficient for large laboratories

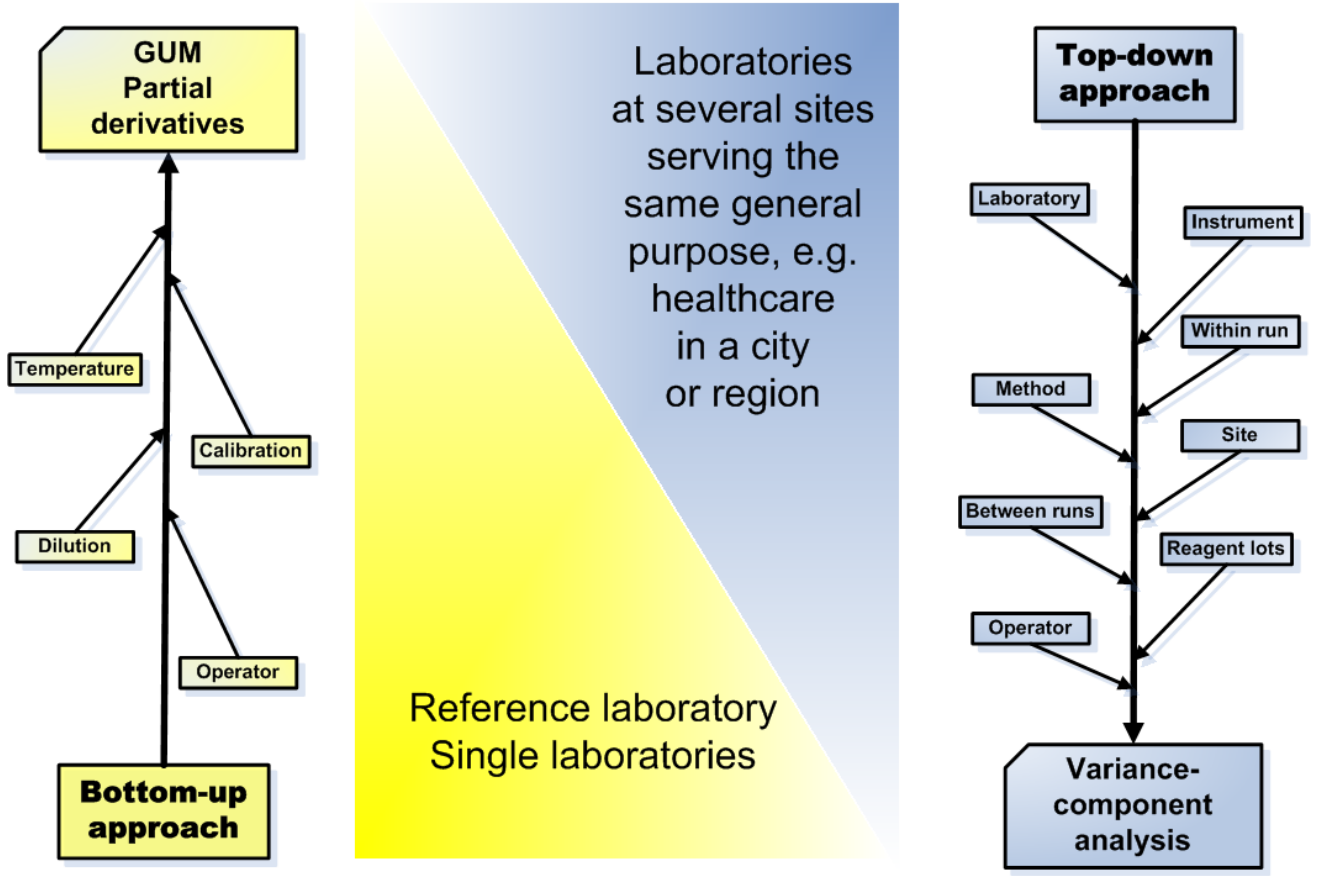
Calculating with bias

1. Identify and eliminate causes of imprecision and bias
2. Calculate uncertainty

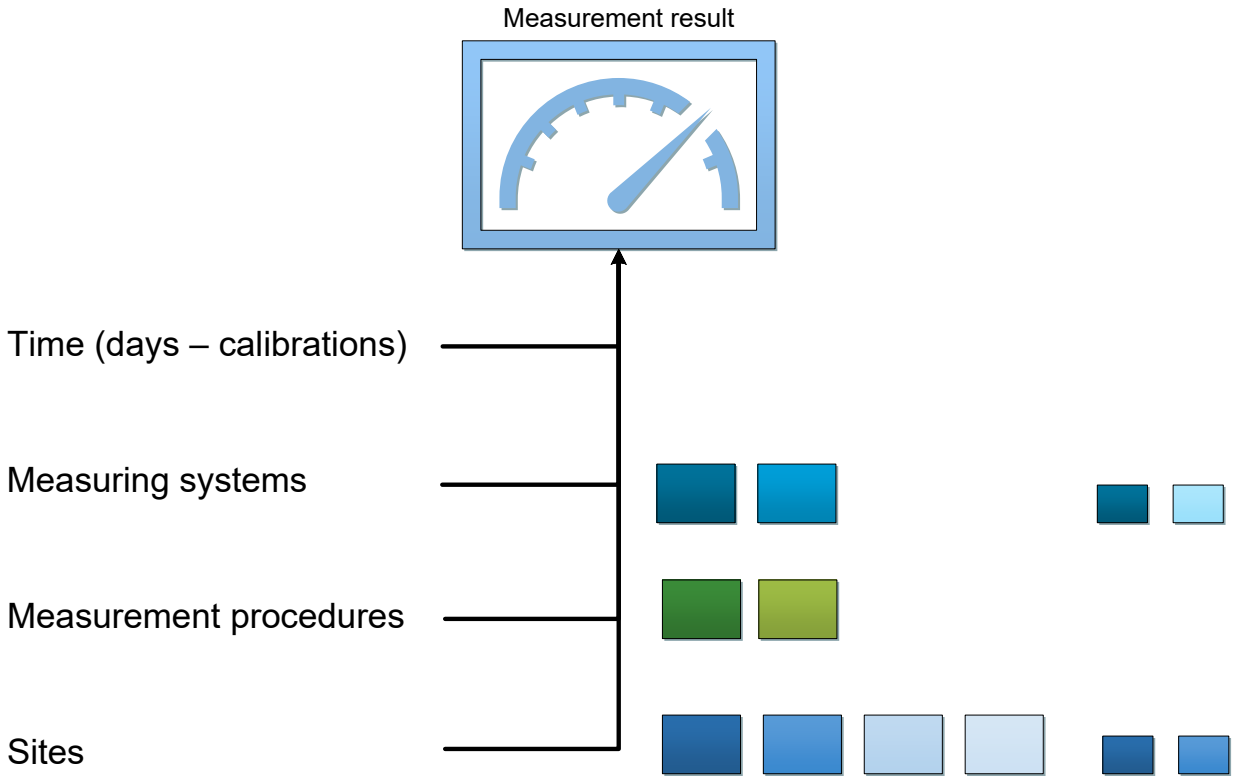
Law of propagation of error

- Calculus for combining uncertainties from multiple variables to estimate uncertainty
  - Simple addition of variances of the various variance components
- Partial derivatives, Taylor series etc.
  - Appropriate for measurement equations

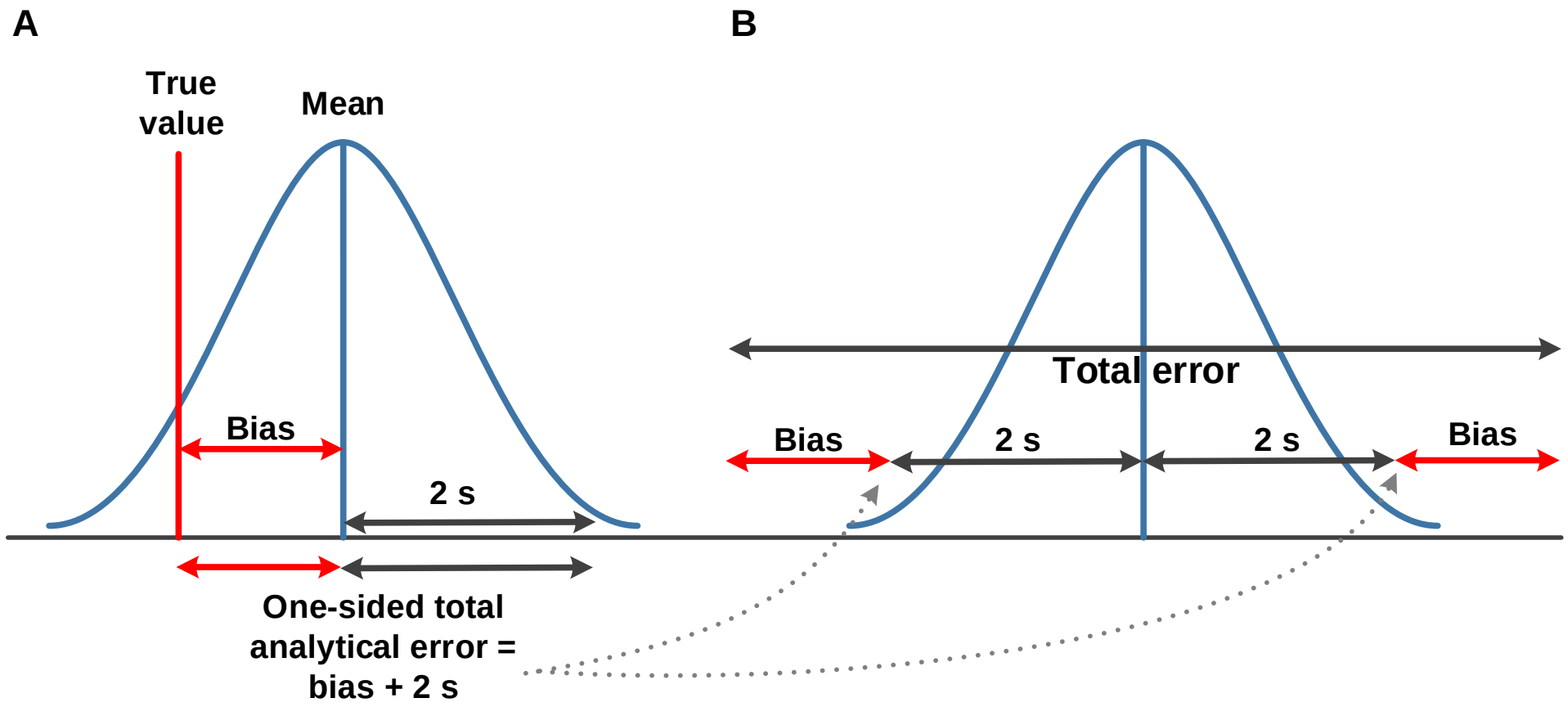
Top down vs Bottom up measure-ment uncertainty



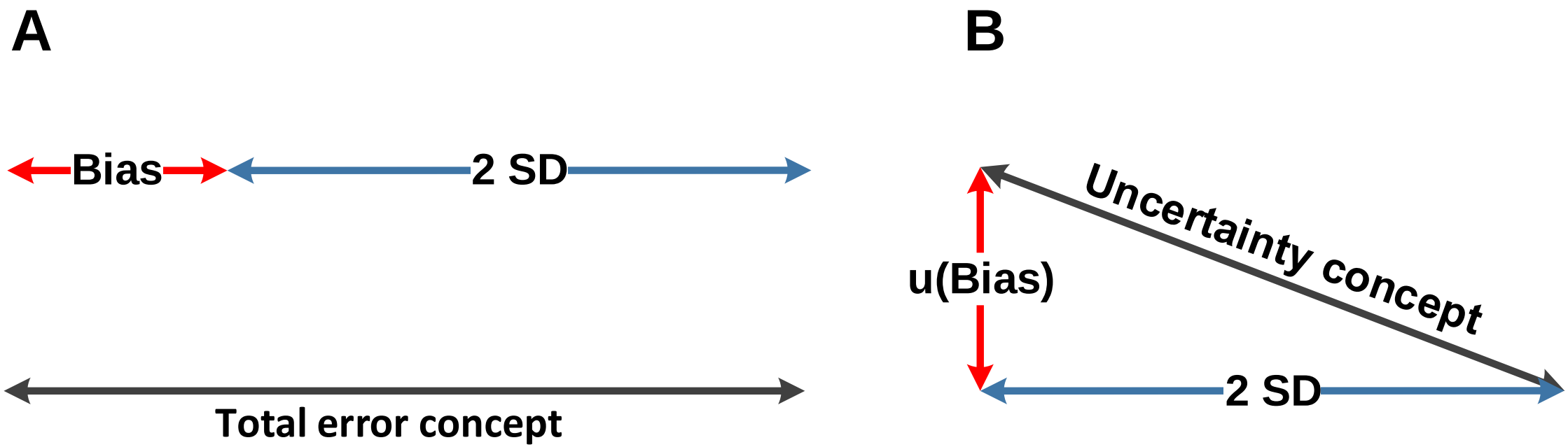
Main factors causing variation in results



Westgard – single and double sided



Adding uncertainties



RiliBÄK- approach (Richtlinien der Bundesärztekammer)

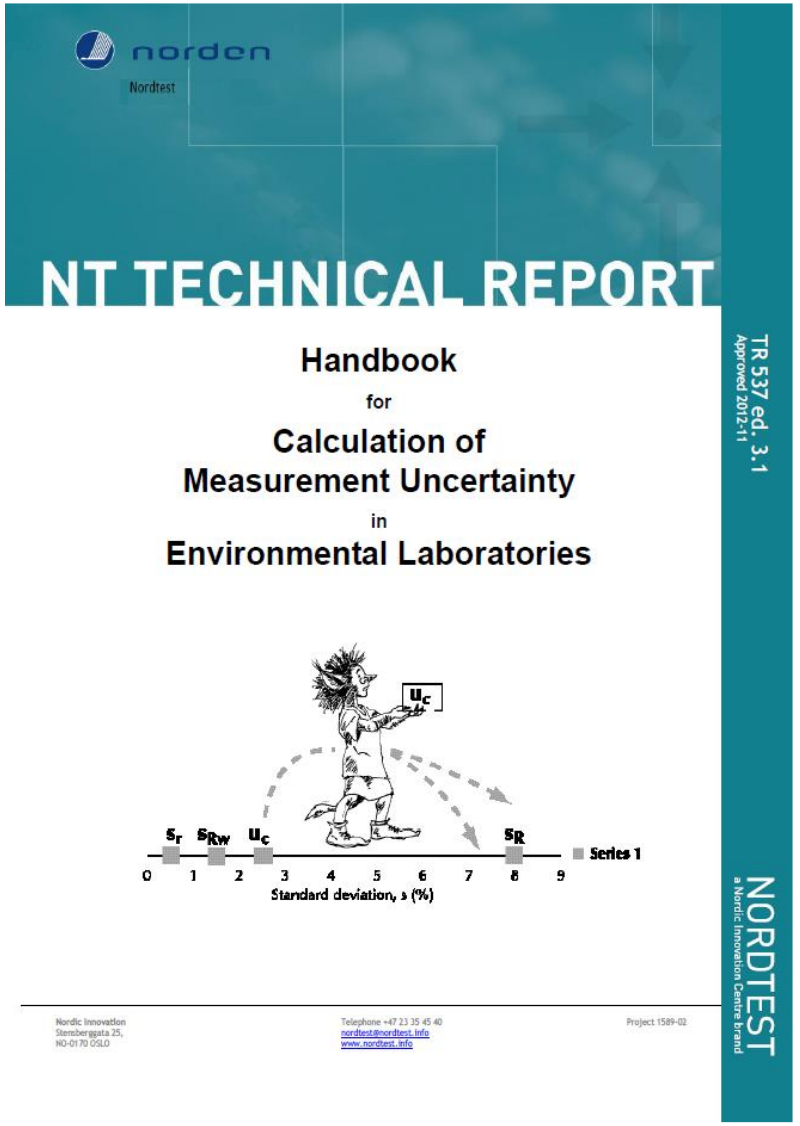
$$\Delta_{max} = \sqrt{k^2 * s^2 + Bias^2}$$

- Δ_{max}=Maximum allowable error when measuring a control sample
- s = standard deviation
- k = a statistical coverage factor which depends on the purpose
- Bias = mean concentration measured in the control samples - target value of the control sample provided by its manufacturer

The TROLL book

Handbook for Calculation of Measurement Uncertainty in Environmental Laboratories

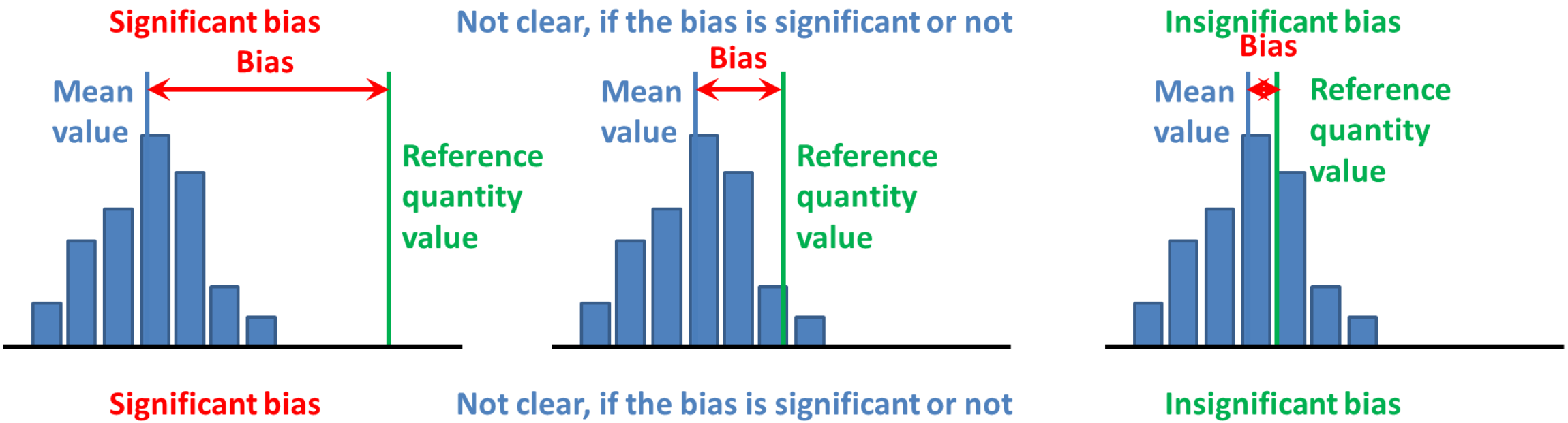
http://www.nordtest.info/index.php/technical-reports/item/handbook-for-calculation-of-measurement-uncertainty-in-environmental-laboratories-nt-tr-537-edition-3.html

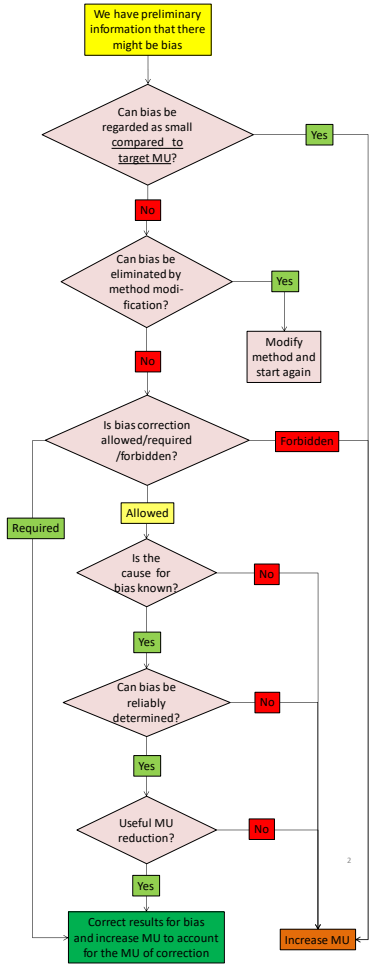


The TROLL book

In Turkish

http://www.nordtest.info/images/documents/nt-technical-reports/NT_TR_537_edition4_Trk.pdf


Significant bias
Bias
Mean value
Reference quantity value
Not clear, if the bias is significant or not
Bias
Mean value
Reference quantity value
Insignificant bias
Bias
Mean value
Reference quantity value
Significant bias
Not clear, if the bias is significant or not
Insignificant bias



There is no point in trying to eliminate or correct a small bias, since both elimination and correction need resources. However it should be considered if the small bias should be taken into account in the MU.

If bias is significant then the best approach, if possible, is to try to eliminate it by modifying the method.

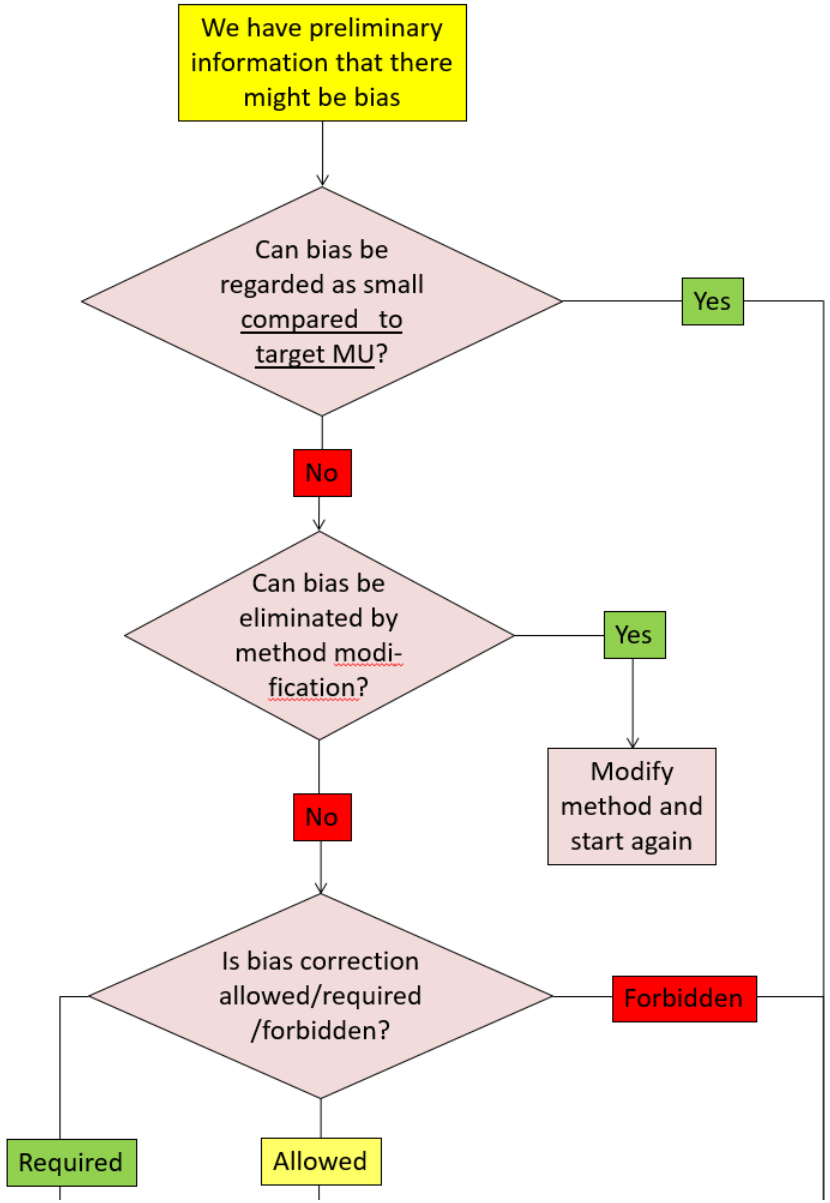
If the bias is significant and eliminating bias is either impossible or impractical then we can consider correcting for bias. There are three possibilities:

1. Correction may be required. If so, we have to correct.
2. Correction can be forbidden. If so, then we cannot correct and we have to take the bias into account as an uncertainty source.
3. Correction may be allowed. Then we will look at three more criteria to determine whether correction is justified.

If the cause of bias is not known then correcting is not recommended and it is more reasonable to include bias into the MU estimate.
Why so? This is because if the cause of bias is not known then in our future results the bias may be absent and if we then correct then we make our result more wrong than it would have been without correction.

If bias cannot be reliably determined then, again, we should not correct for it, because if we correct the result with an unreliable bias estimate then we can make it more wrong than it would have been without correction.

Correcting for bias is meaningful only if eventually useful reduction of MU is achieved (considering that correcting, while removing bias, also introduces additional uncertainty). If useful uncertainty reduction is not achieved then bias correction is not justified and it should rather be included in uncertainty



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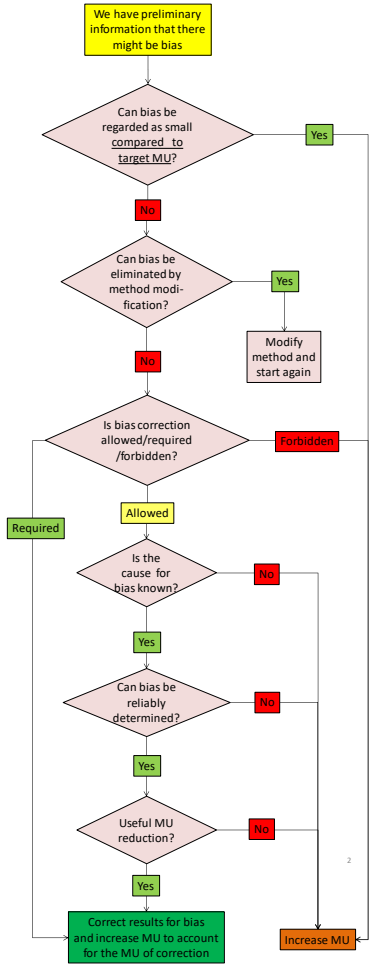

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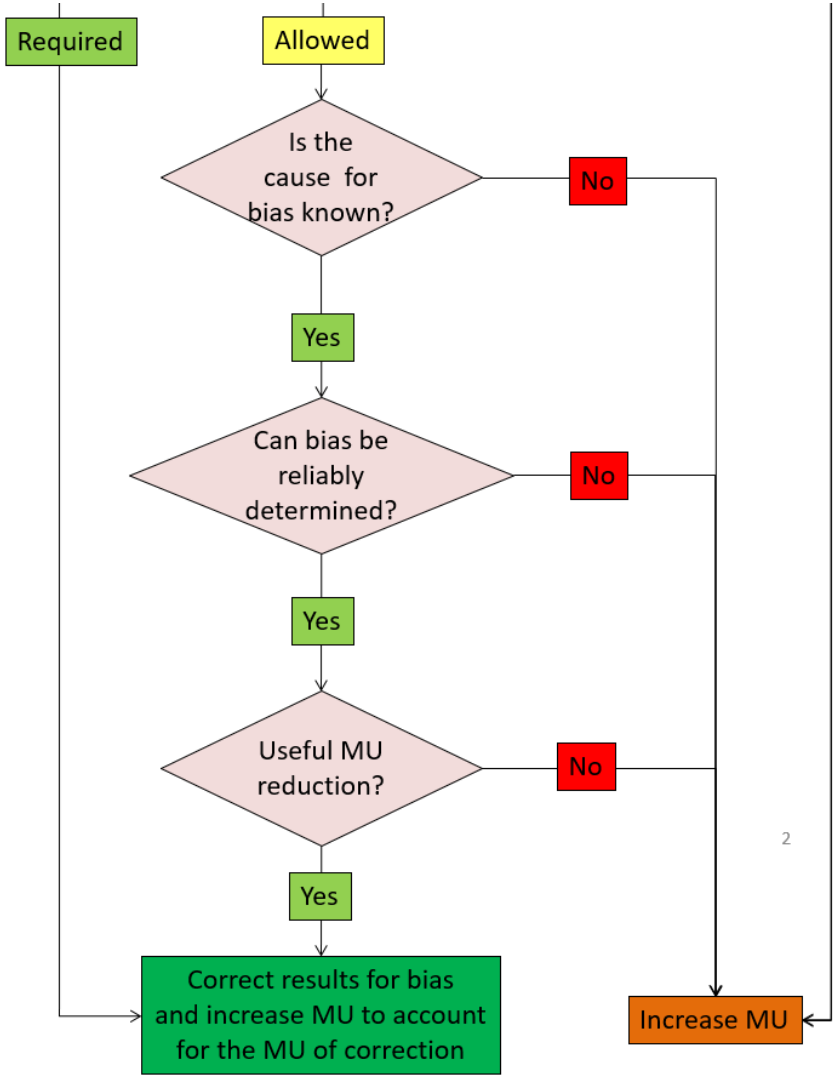

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Relative standard uncertainty

- The standard deviation divided by the mean
- %CV is that figure expressed as percent

100	-0.5	0.25	1000	-5	25
101	0.5	0.25	1010	5	25
100	-0.5	0.25	1000	-5	25
99	-1.5	2.25	990	-15	225
101	0.5	0.25	1010	5	25
102	1.5	2.25	1020	15	225
99	-1.5	2.25	990	-15	225
100	-0.5	0.25	1000	-5	25
101	0.5	0.25	1010	5	25
102	1.5	2.25	1020	15	225
100.50	Mean		1005.00	Mean	
1.08	SD		10.80	SD	
1.07	%CV		1.07	%CV	
0.34	SEM		3.42	SEM	

Root mean square bias

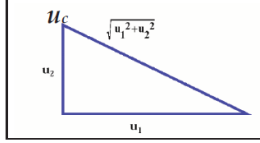
- $RMS_{bias} = \sqrt{\frac{\sum(bias_i)^2}{n}}$

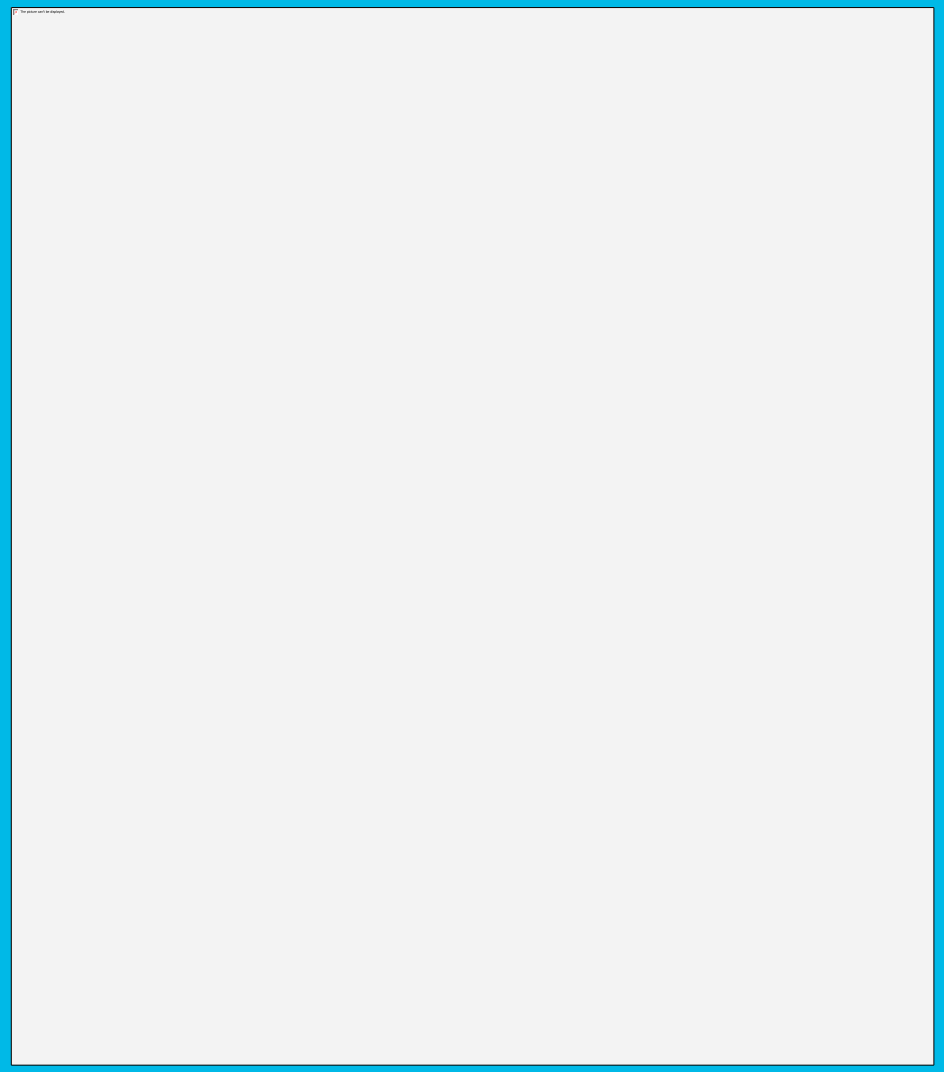
Relative root mean square bias

- RMS_{bias} divided by the mean

Add relative variances
=
Add relative standard deviations squared

Magnusson, B., et al. (2012). "Routine internal- and external-quality control data in clinical laboratories for estimating measurement and diagnostic uncertainty using GUM principles." Scand J Clin Lab Invest **72**(3): 212-220.

Step	Action	Lower interval < 120 µmol/L	Higher interval > 120 µmol/L
1	*Specify Measurand*	Concentration of creatinine in a serum sample delivered to the laboratory.	
2	*Quantify* R_w *component* *A control sample*	s_{Rw} = 3.4 µmol/L	CV_{Rw}=3.7 %
3	*Quantify bias components*	RMS_{bias} = 5.1 µmol/L $u(C_{Ref})$ = 0.7 µmol/L	RMS_{bias} = 3.0 % $u(C_{Ref})$ = 0.5 %
4	*Convert components to standard uncertainty u(x)*	$u(R_w) = s_{Rw}$ = 3.4 µmol/L $u(\text{bias}) = \sqrt{RMS_{bias}^2 + u(C_{ref})^2}$ $= \sqrt{5.1^2 + 0.7^2}$ µmol/L = 5.1 µmol/L	$u(R_w) = CV_{Rw}$ = 3.7 % $u(\text{bias}) = \sqrt{RMS_{bias}^2 + u(C_{ref})^2}$ $= \sqrt{3.0^2 + 0.5^2}$ % = 3.0 %
5	*Calculate combined standard uncertainty,* 	Standard uncertainties can be summed by taking the square root of the sum of the squares $u_c = \sqrt{u(R_w)^2 + (u(\text{bias}))^2}$ $= \sqrt{3.4^2 + 5.1^2}$ µmol/L = 6.1 µmol/L	$u_c = \sqrt{u(R_w)^2 + (u(\text{bias}))^2}$ $= \sqrt{3.0^2 + 3.7^2}$ % = 4.8 %
6	*Calculate expanded uncertainty,* $U = 2 \cdot u_c$	The measurement result the expanded uncertainty gives an interval where the "true value" lies with a high enough confidence (app. 95 %). $U = 2 \cdot 6.1$ µmol/L = 12.2 µmol/L ≈ 12 µmol/L	$U = 2 \cdot 4.5\,\% = 9.6\,\% \approx 10\,\%$



Thank you

www.liu.se

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