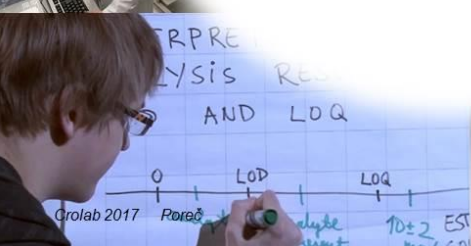


LC-MS Method Validation On-line course

https://sisu.ut.ee/lcms_method_validation/



Ten years of web-based teaching – what have we learned?



Co-funded by the Erasmus+ Programme of the European Union

Ivo Leito
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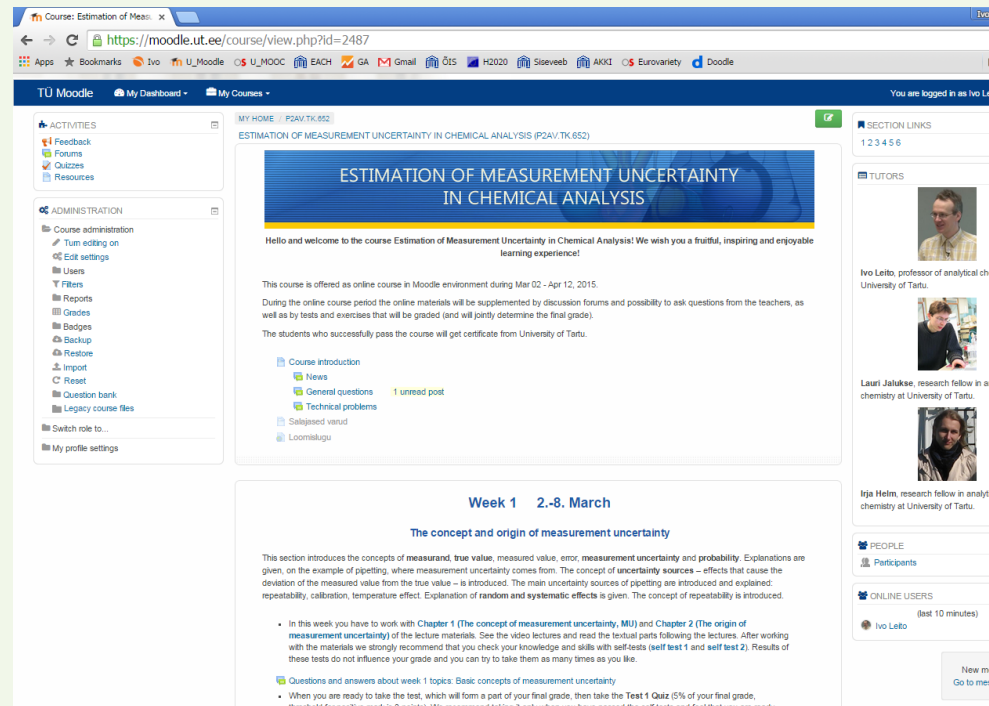
sisu.ut.ee/measurement
sisu.ut.ee/lcms_method_validation

www.analyticalchemistry.eu

28.06.2023

Eurovariety 2023

Tartu



Questions we will discuss

- To what extent can a **web course** be a **substitute for face-to-face** teaching?
– *Massive Open Online Courses (MOOCs)*
- Lessons learned from **running an international master's programme**?
- Was the **COVID pandemic** only bad?
- Please ask questions at any moment

Web courses

Joint MSc programme

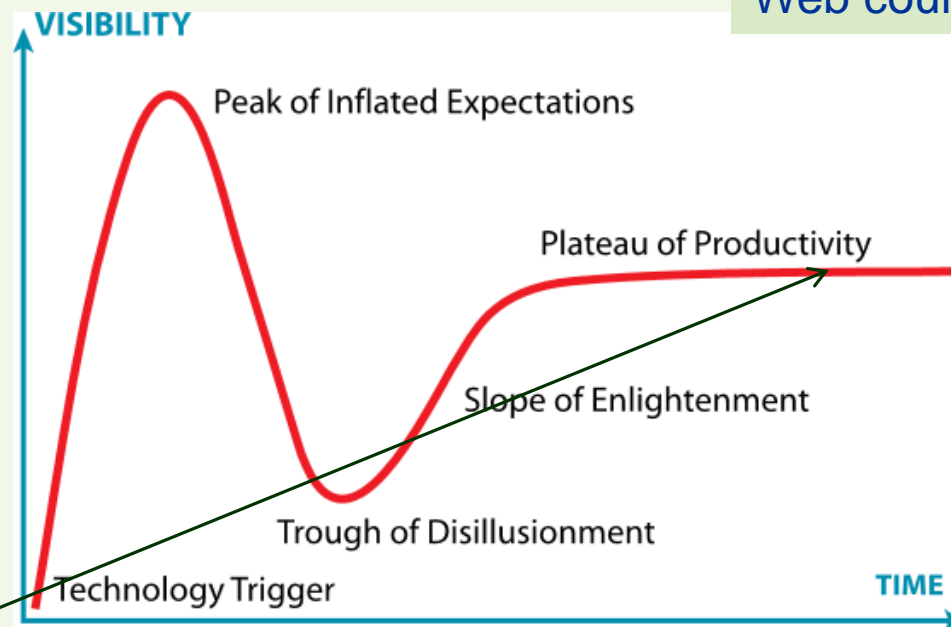
Massive Open Online Courses

- Term coined in 2008
 - by D. Cormier and G. Siemens
- MOOCs were hailed as the **future of higher education**
 - 2012: „Year of the MOOC“ by NYT
- Since then, a lot of criticism
 - insufficient interaction between teachers and students, low course completion rates, etc
 - It is acknowledged that MOOCs **were originally overhyped**

Cormier D (2008) *The CCK08 MOOC – connectivism course, 1/4 way*. Available from Dave Cormier's blog. <http://davecormier.com/edblog/2008/10/02/the-cck08-mooc-connectivism-course-14-way/>

Pappano L (2012) The year of the MOOC. *The New York Times*, Nov 2, 2012

MOOCs: where are we now?



MOOCs are approximately here

"Gartner Hype Cycle" by Jeremykemp at English Wikipedia.
Licensed under CC BY-SA 3.0 via Wikimedia Commons

- Our experience:
MOOCs have **undoubted virtues**

On-line course: Estimation of measurement uncertainty in chemical analysis



ESTIMATION OF MEASUREMENT UNCERTAINTY IN CHEMICAL ANALYSIS

Course introduction

1. The concept of measurement uncertainty (MU)

Self-test 1

2. The origin of measurement

3. The first uncertainty quantification

5. Principles of measurement uncertainty estimation

6. Random and systematic effects revisited

7. Precision, trueness, accuracy

8. Overview of measurement uncertainty estimation approaches

9. The ISO GUM Modeling approach

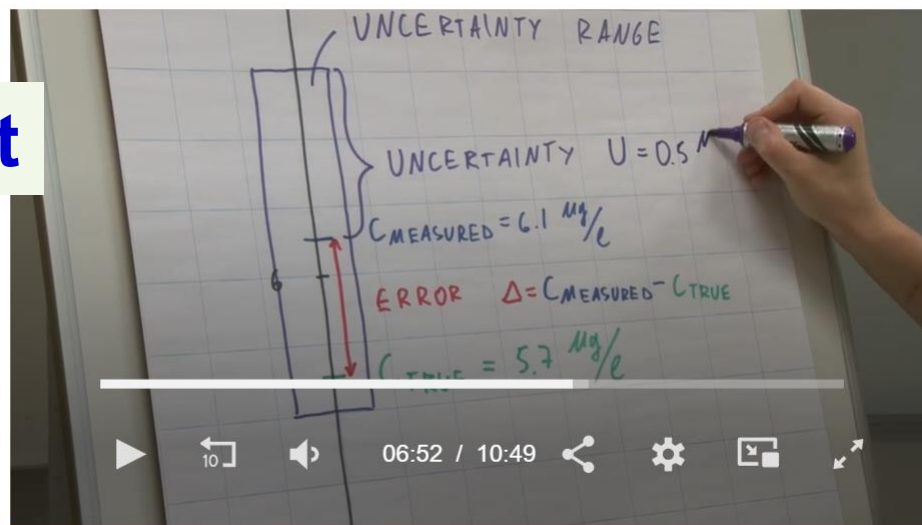
10. The single-lab validation approach

11. Comparison of the approaches

12. Comparing measurement results

1. THE CONCEPT OF MEASUREMENT UNCERTAINTY (MU)

Brief summary: This section introduces the concepts of measurand, true value, measured value, error, measurement uncertainty and probability.



The concept of measurement uncertainty

<http://www.utv.ee/naita?id=17583>

<https://www.youtube.com/watch?v=BogGbA0hC3k>

Measurement is a process of experimentally obtaining the value of a quantity. The quantity that we intend to measure is called **measurand**. In chemistry the measurand is usually the content (concentration) of some chemical entity (molecule, element, ion, etc) in some object. The chemical

sisu.ut.ee/measurement

Teaching measurement uncertainty

- **Notoriously difficult**

It is usually taught at the level of basics but difficulties emerge first of all with practical applications

- Usually taught in connection with analytical chemistry
- Many guideline materials and courses
- **Most training courses stop exactly at the moment when it gets „interesting“**

Features

- Main measurement uncertainty concepts
- Two main uncertainty estimation approaches are **discussed in depth** and **compared**
- Video tutorials of **uncertainty calculations**
- Numerous **Practical examples**

sisu.ut.ee/measurement

On-line course: LC/MS Method Validation

Validation of liquid chromat... x

https://sisu.ut.ee/lcms_method_validation/

UNIVERSITY OF TARTU

LC-MS METHOD VALIDATION

Course introduction

1. Validation: General
2. Selectivity and identity confirmation
3. Linearity of signal, linear range, sensitivity
4. Precision
5. Trueness
6. Precision and trueness: some additional aspects
7. Accuracy
8. Stability
9. LoD and LoQ
10. Ruggedness, robustness

VaLChrom

Acknowledgements

References

Glossary

What our participants say?

0:00 / 2:23

Course introduction

<http://www.utv.ee/naita?id=23245>

<https://www.youtube.com/watch?v=jbdA8PnPdLY>

Short description of the course

This is a practice-oriented on-line course on validation of analytical methods, specifically using LC/MS as technique. The course introduces the main concepts and mathematical apparatus of validation, covers the most important method performance parameters and ways of estimating them. The course is largely based on the recently published two-part tutorial review:

LC-MS as technique

- No 1 technique for determination of **low levels** of organics in **difficult matrices**
 - Biomedical, environmental, „-omics“, ...
- LC-MS: **many adjustable parameters**
 - In LC
 - In MS

Checking that the method performs as required is not trivial!


Validation is BIG in LC-MS!

Guidelines?

Web courses

NordVal Protocol Document 9

NordVal Protocol No. 2, Approved 26 May 2010



Guide in Validation of Alternative Proprietary Chemical Methods

VALIDATION AND EVALUATION OF QUALITATIVE PROPRIETARY METHODS	2
METHOD COMPARISON STUDY	5
INTERMEDIATE STUDY	9
INTERPRETATION	9
PART 2: VALIDATION AND EVALUATION OF QUANTITATIVE PROPRIETARY METHODS	10
A. METHOD COMPARISON STUDY	10
B. INTERMEDIATE STUDY	14
REFERENCES	15

Pure Appl. Chem., Vol. 74, No. 5, pp. 835–855, 2002
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INTERNATIONAL UNION OF PURE AND APPLIED CHEMISTRY
ANALYTICAL, APPLIED, CLINICAL, INORGANIC, AND
PHYSICAL CHEMISTRY DIVISIONS
INTERDIVISIONAL WORKING PARTY FOR HARMONIZATION OF
QUALITY ASSURANCE SCHEMES FOR ANALYTICAL LABORATORIES*

HARMONIZED GUIDELINES FOR SINGLE-LABORATORY VALIDATION OF METHODS OF ANALYSIS

(IUPAC Technical Report)

from the Symposium on Harmonization of Quality Assurance Systems for Analytical Laboratories, Budapest, Hungary, 4–5 November 1995, held under the sponsorship of IUPAC, ISO, and AOAC International

Prepared for publication by
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European Medicines Agency

London, 19 November 2009
Doc Ref EMEA/CHMP/ENP/192217/2009

COMMITTEE FOR MEDICINAL PRODUCTS FOR HUMAN USE (CHMP)

DRAFT

GUIDELINE ON VALIDATION OF BIOANALYTICAL METHODS	September 2009
DRAFT AGREED BY THE EFFICACY WORKING PARTY	19 November 2009
ADOPTION BY CHMP FOR RELEASE FOR CONSULTATION	31 May 2010

END OF CONSULTATION (DEADLINE FOR COMMENTS)

Comments should be provided using the template to EDPs@ema.europa.eu


KEYWORDS: CHMP, EMEA, Guideline, validation, bioanalytical method, analyses

HARMONISED TRIPARTITE GUIDELINE ON HARMONISATION OF TECHNICAL VALIDATION OF PHARMACEUTICALS FOR HUMAN USE

VALIDATION OF ANALYTICAL PROCEDURES: TEXT AND METHODOLOGY Q2(R1)

Current Step 4 version
Parent Guideline dated 27 October 1994
(Complementary Guideline on Methodology dated 6 November 1996 incorporated in November 2005)

This Guideline has been developed by the appropriate ICH Expert Working Group and has been subject to consultation by the regulatory bodies, in accordance with the ICH Process. At Step 4 of the Process the final draft is recommended for adoption to the regulatory bodies of the European Union, Japan and USA.



A Focus for Analytical Chemistry in Europe

The Fitness for Purpose of Analytical Methods

A Laboratory Guide to Method Validation and Related Topics

Guidance for Industry Bioanalytical Method Validation

Additional copies are available from:

Office of Communications
Division of Drug Information, FDA, Room 2201
Center for Drug Evaluation and Research
Food and Drug Administration
10901 New Hampshire Ave., Silver Spring, MD 20993
Phone: 301-796-3400, Fax: 301-847-8714
druginfo@fda.hhs.gov
<http://www.fda.gov/oc/communications/communications/communications/default.htm>

and/or

Communications Staff, HFPI-12
Center for Veterinary Medicine
Food and Drug Administration
7519 Standish Place, Gaithersburg, MD 20885
(761) 240-1760/2160
<http://www.fda.gov/cvm/communications/communications/communications/default.htm>

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Veterinary Medicine (CVM)

September 2013
Biopharmaceutics

Revision 1

Validation guidelines

- Guidelines are useful, but ...
 - Sometimes very **general**
 - How many replicates? Which spiking levels?
How many days? ...
 - Sometimes **different** recommendations
 - Usually **LC-MS is not addressed**
 - Except e.g. 2002/657/EC, SANTE
 - Sometimes **advanced calculations** are required

Validation in LC-MS is not easy!

Features

- Main validation guidelines are **reviewed** and **compared**
 - With every performance parameter
- **Recommendations** are given how to determine performance parameters
 - Synthesis from guidelines and our experience
- Specific **LC-MS issues**
 - Ionization, matrix effects, MSⁿ selectivity, ...
- **General workflow** of LC-MS method validation is presented

Our goal with both courses

- Web-based teaching material for
 - **Independent** learning
 - Knowledge applicable **in real-life situations**
 - On-line **reference point** of explanations of concepts and approaches
 - **Support for auditorial teaching** of metrology in chemistry at UT
 - Offering as **MOOCs**
 - **Promoting** our analytical chemistry education

Course contents

- **Theoretical** basis as well as **practical** skills
- **Detailed** and **example**-based treatment
- **Tens** of short **video lectures**
 - Supplemented by textual explanations and downloadable slides and calculation files
- Numerous online **tests** and **calculation exercises**
 - Understanding of main concepts
 - Calculation exercises from **real life** situations
 - **Feedback** is given
- **Forums**

I. Leito, I. Helm. Metrology in chemistry: some questions and answers.
J. Chem. Metrol. **2020**, *14*, 83–87

Platforms

- Course contents:
sisu.ut.ee/measurement
sisu.ut.ee/lcms_method_validation

- Admin, forums, knowledge evaluation:
moodle.ut.ee



Course: Estimation of Meas... x

<https://moodle.ut.ee/course/view.php?id=2487>

TU Moodle My Dashboard My Courses You are logged in as Ivo Leito (Log out)

ACTIVITIES
 Feedback
 Forums
 Quizzes
 Resources

ADMINISTRATION
 Course administration
 Turn editing on
 Edit settings
 Users
 Filters
 Reports
 Grades
 Badges
 Backup
 Restore
 Import
 Reset
 Question bank
 Legacy course files
 Switch role to...
 My profile settings

MY HOME (P24V:TK:652)
 ESTIMATION OF MEASUREMENT UNCERTAINTY IN CHEMICAL ANALYSIS (P24V:TK:652)

SECTION LINKS
 1 2 3 4 5 6

TUTORS
 Ivo Leito, professor of analytical chemistry at University of Tartu.
 Lauri Jahuake, research fellow in analytical chemistry at University of Tartu.
 Iija Heim, research fellow in analytical chemistry at University of Tartu.

PEOPLE
 Participants

ONLINE USERS
 (last 10 minutes)
 Ivo Leito

ESTIMATION OF MEASUREMENT UNCERTAINTY IN CHEMICAL ANALYSIS

Hello and welcome to the course Estimation of Measurement Uncertainty in Chemical Analysis! We wish you a fruitful, inspiring and enjoyable learning experience!

This course is offered as online course in Moodle environment during Mar 02 - Apr 12, 2015. During the online course period the online materials will be supplemented by discussion forums and possibility to ask questions from the teachers, as well as by tests and exercises that will be graded (and will jointly determine the final grade). The students who successfully pass the course will get certificate from University of Tartu.

Course introduction
 News
 General questions 1 unread post
 Technical problems
 Skipped version
 Loomilugu

Week 1 2.-8. March
 The concept and origin of measurement uncertainty

This section introduces the concepts of measurand, true value, measured value, error, measurement uncertainty and probability. Explanations are given, on the example of pipetting, where measurement uncertainty comes from. The concept of uncertainty sources – effects that cause the deviation of the measured value from the true value – is introduced. The main uncertainty sources of pipetting are introduced and explained: repeatability, calibration, temperature effect. Explanation of random and systematic effects is given. The concept of repeatability is introduced.

In this week you have to work with Chapter 1 (The concept of measurement uncertainty, MU) and Chapter 2 (The origin of measurement uncertainty) of the lecture materials. See the video lectures and read the textual parts following the lectures. After working with the materials we strongly recommend that you check your knowledge and skills with self-tests (self test 1 and self test 2). Results of

Uncertainty course completion statistics

	2014	2015	2016	2017	2018	2019	2020	2021	2022	2023	Total
Registered participants	271	489	760	363	521	590	843	950	851	993	6631
Successfully finished	141	169	308	148	218	238	464	314	239	333	2572
Active participants	201	272	455	216	358	381	600	501	405	523	3912
Successfully finished %	52%	35%	41%	41%	42%	40%	55%	33%	28%	34%	39%
Participated %	74%	56%	60%	60%	69%	65%	71%	53%	48%	53%	59%
Successfully finished % (active participants)	70%	62%	68%	69%	61%	62%	77%	63%	59%	64%	66%
Number of countries	40	70	85	69	70	86	95	97	103	99	149

- Next edition: will start in March 2024
- Registration link will be in Jan 2024 at:

sisu.ut.ee/measurement

Validation course completion statistics

	2017	2018	2019	2020	2021	2022	2023	Total
Registered participants	303	424	426	515	791	850	903	4212
Successfully finished	168	159	125	161	221	209	218	1261
Active participants	224	236	227	267	338	380	376	2048
Successfully finished %	55%	38%	29%	31%	28%	25%	24%	30%
Participated %	74%	56%	53%	52%	43%	45%	42%	49%
Successfully finished % (active participants)	75%	67%	55%	60%	65%	55%	58%	62%
Number of countries	61	71	70	77	86	97	104	128

- Next edition: will start in Nov 2023
- Registration link will be in Sept 2023 at:

sisu.ut.ee/lcms_method_validation/

MOOCs vs „traditional“ teaching

Aspect	Conventional university course	Practitioner training (short) course	MOOC
Interaction between students and teachers	Direct	Direct	Remote
Possibility to deliver the course simultaneously to many participants	Low	Low	High
Level of self-discipline needed from participants	Average	Average	High
Time constraints, time to “digest” the knowledge	Not a problem	Serious time constraints	Not a problem
Possibility of independent homework	Possible	Usually impossible	Possible
Possibility of hands-on problem-solving	Possible	Possible (within the time constraints)	Possible
Possibility of teamwork	Possible	Possible (within the time constraints)	Not easy
Possibility of experimental work	Easy	Possible, but not easy	Not possible
Possibility of working with participants of uneven level or preparation	Difficult but doable	Difficult	Possible
Possibilities of meaningful assessment of obtained knowledge	Wide possibilities	Difficult	Possible
Danger of cheating during knowledge assessment	Can be made low	Can be made low	Can be high
Costs of setting up the course ^a	Medium	Medium	Medium
Costs of running the course ^a	High	High	Low
Travel and accommodation costs	Can be high	Can be high	None

Measurement Uncertainty and Method Validation web courses

University teaching

On-line course for independent learning

available any time anywhere

Course material
for running training courses e.g. by labs

Information source

On-line reference point

of terminology, explanations and self-testing possibilities

Support to university teaching

Students can be directed here e.g. for self-testing

MOOC

Ordinary MOOC

with registered participation, on-line counseling, graded tests and certificate

Running as hybrid course

partly auditorial, partly on-line



Excellence in Analytical Chemistry

- Started in 2015 by four European universities:



*Fundamentals of analytical chemistry,
metrology in chemistry, quality assurance,
socio-economic aspects*



UPPSALA
UNIVERSITET

*Organic and bioorganic analysis,
advanced separation methods, mass
spectrometry*



*Industrial analysis, process
control and monitoring*



Åbo Akademi
University

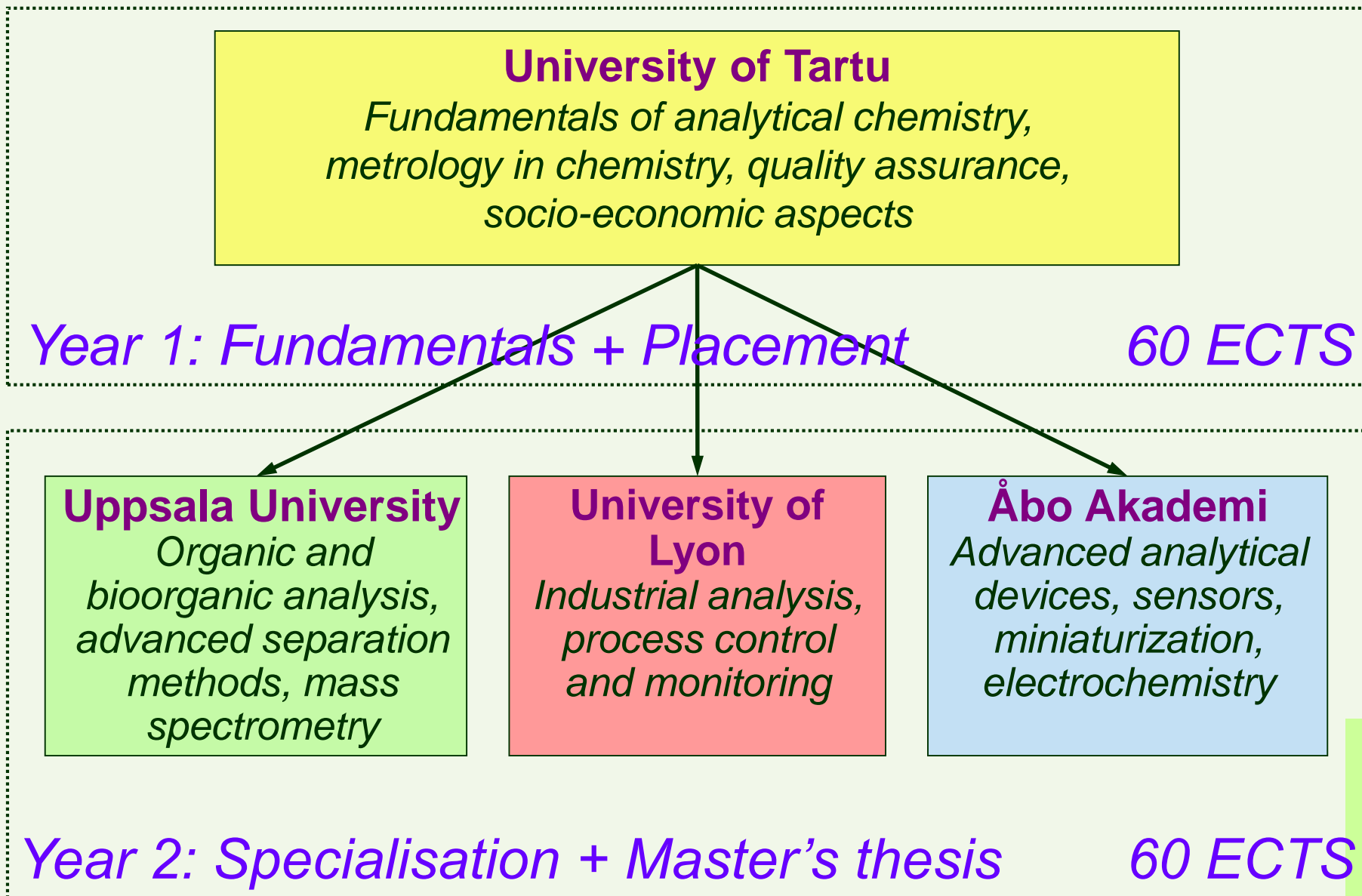
*Advanced analytical devices,
sensors, miniaturization,
electrochemistry*



- **Full-fledged contemporary analytical master degree programme (120 ECTS)**
 - Highly international
- Tuned to the **job market** needs
 - Practical placement
 - Socio-economic aspects
 - Metrology topics
 - „Research-grade“ master’s thesis
- **Funded by the EU’s *Erasmus Mundus* scheme**
 - In most classes between 20 and 30 students

I. Leito, A. Teearu, J. Bobacka, J. Randon, J. Bergquist. EACH (Excellence in Analytical Chemistry), an Erasmus Mundus Joint Programme: progress and success. *Anal. Bioanal. Chem.* **2019**, 411, 5913–5921

Programme structure:

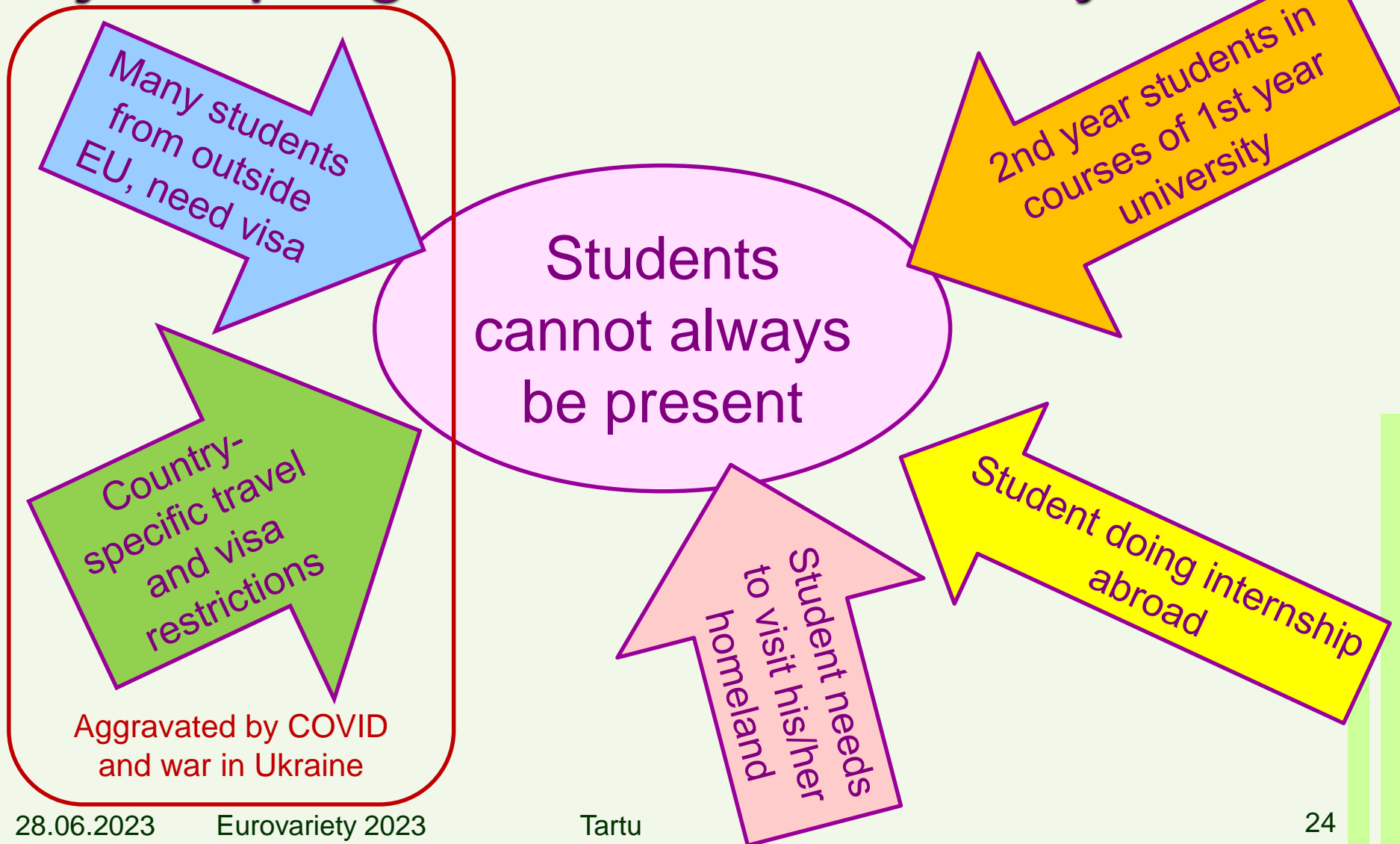


EACH Academic leaders at second year universities

- Prof. Jonas Bergquist (UU)
 - A worldwide leader in biomedical LC and MS
- Prof. Jérôme Randon (UCBL)
 - Founder of the unique industrial analysis programme at Lyon
- Prof. Johan Bobacka (AAU)
 - His work on electrochemical sensors is „probing“ the future of analytical chemistry



Some issues with organizing a joint programme with mobility



COVID and analytical chemistry teaching in EACH

- The online infrastructure, experience and technical support were there before COVID

**Many thanks to education technology
people at UT!**

- Helped to avoid big gaps
- Lectures and exams were run online
 - Via Moodle/BBB
- Some (although limited) help for labs

- Lectures and seminars in **hybrid** mode
 - Illnesses, internships, mobility ...
 - Somewhat more work
- More **Polling** during lecture
 - Engagement
 - Early discovery of problems
- Lectures **recorded**
 - Illnesses, internships, mobility ...
 - Some explanation may have been better last year

COVID's legacy?

COVID started several
of these things

We still do all of them
now!

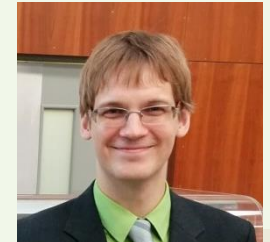
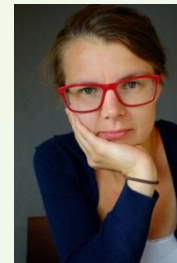
COVID's *legacy?*

- Slides with a lot of **missing information**
 - More engagement
 - Good ideas
- More **on-line (self)tests**
 - Engagement
 - Early discovery of problems
- **Oral exams**
 - More fair grading
 - Limited possibilities for cheating
 - Internships, mobility ...
 - **More work**

Big thank you to the MOOC team!

Core team

Irja Helm, Lauri Jalukse, Anneli Kruve,
Koit Herodes, Maarja-Liisa Oldekop,
Riin Rebane, Karin Kipper, Hanno Evard



Video, design, IT, admin

Enno Kaasik, Triin Marandi, Lehti Pilt,
Esta Pilt, Toomas Petersell



*Many thanks to the **EACH** team!*

Jonas Bergquist, Jérôme Randon, Johan Bobacka,
Ülle Tensing, Anu Teearu, Koit Herodes, Irja Helm,
Sigrid Selberg, Martin Vilbaste, Hanno Evard,
Erko Jakobson, Astrid Darnell, Magnus Strandås,
Sofia Thorsélius, Heidi Karlsson, Dana-Maria Daia,
Cinzia Cecchetto, Emilie Noguez, ...

Thanks to:



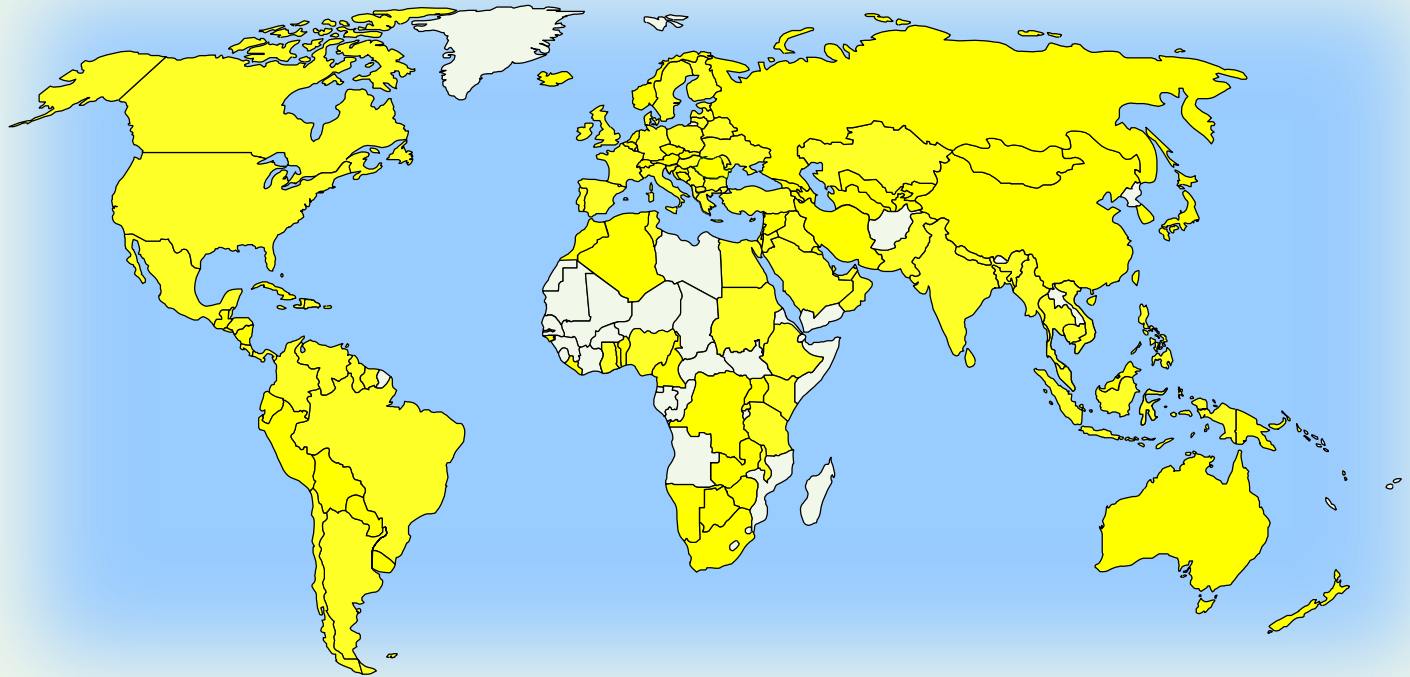
Co-funded by the
Erasmus+ Programme
of the European Union

Full information:
www.analyticalchemistry.eu

Many thanks for your attention!

MOOCs' Top countries By number of participants:

Philippines	989
Poland	912
Estonia	716
Brasil	551
Egypt	361
France	358
Trinidad and Tobago	308
Spain	297
Serbia	243
USA	237



153 countries overall