Establishing Metrology Standards in Microfluidic Devices

Développement de normes de métrologie pour les dispositifs microfluidiques

Florestan Ogheard (CETIAT)
Elsa Batista (IPQ)
Vania Silverio (INESC MN)
Christina Pecnik (IMTAG)
Elena Muller (MicrofluidicChipShop)
Anders Niemann (DTI)

MFMET
Establishing Metrology Standards in Microfluidic Devices

EMPIR EURAMET

The EMPIR initiative is co-funded by the European Union's Horizon 2020 research and innovation programme and the EMPIR Participating States

Summary

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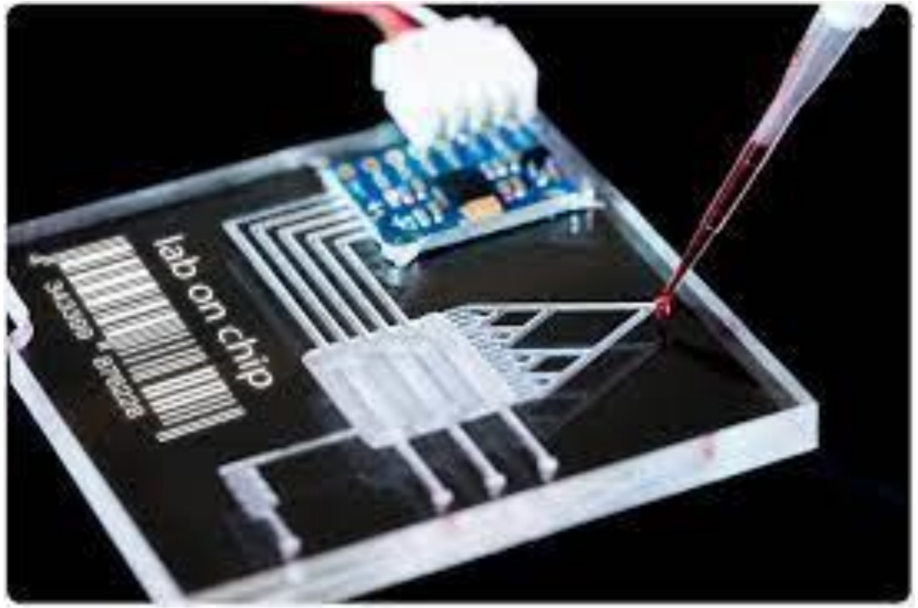
- What is Microfluidics ?
- EMPIR project 20NRM02 MFMET
    - Overview and goals
    - Work package achievements including experimental results on microfluidics metrology
- Conclusions



Microfluidics

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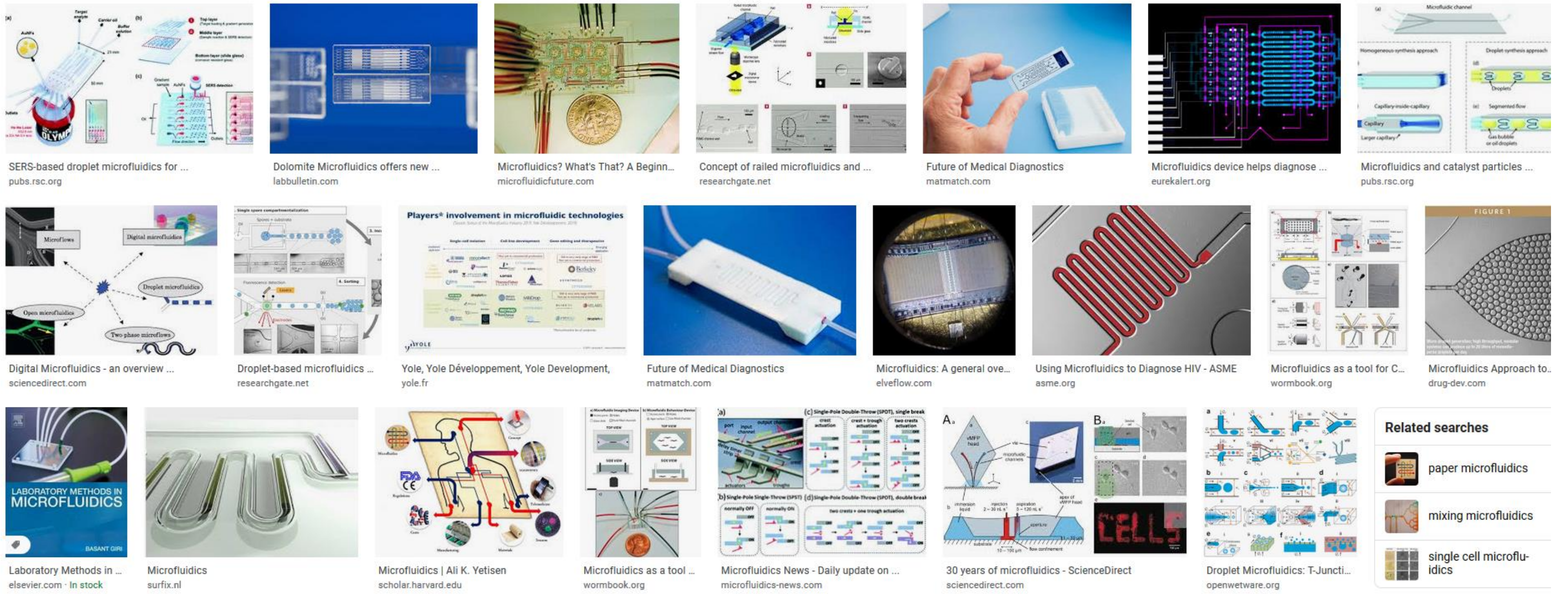
Microfluidics is both the science which studies the behavior of fluids through microchannels and the technology of manufacturing microminiaturized devices containing chambers and channels through which fluids flow or are confined.



Microfluidic devices are **small**, **simple to use**, **portable** and can be used in several emerging applications such as micro-liquid chromatography, (scaled down) process technology or micro-reactors, drug development, micro-implantology, Lab-on-a-chip, etc.

It is crucial that volume and flow in these devices are as ACCURATE and PRECISE as possible, therefore we need APPROPRIATE CALIBRATION METHODS and Standards

EMPIR MFMET Overview

Call: 2020 Normative

JRP name: Establishing metrology standards in microfluidic devices

JRP refeence: 20NRM02 MFMET

Total budget: ~ 1 M€

Total labour: ~120 MM

Duration: 36 months

Start date: June 2021

Coordinating Organisation: IPQ

Partners - 9 NMIs/DIs, 4 research institutions/university, 4 companies (17). 12 countries

Collaborators: 27

Chief stakeholder: The Microfluidic association

https://mfmet.eu, more than 2000 viewers per month
https://zenodo.org/communities/mfmet

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MFMET Consortium

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University of Glasgow

Bronkhorst® Flow Technology

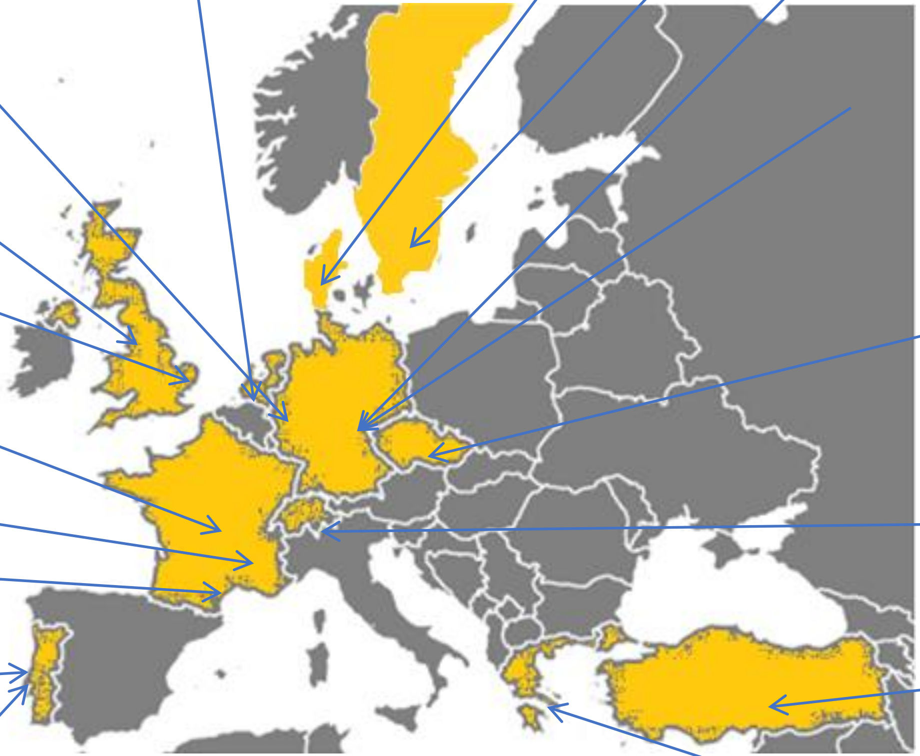
enabling MNT micro nano technology

DANISH TECHNOLOGICAL INSTITUTE

RISE Research Institutes of Sweden

Hahn Schickard

TÜV SÜD
National Engineering Laboratory



microfluidic ChipShop

CZECH METROLOGY INSTITUTE

leti ceatech

CETIAT ensemble, innover et valider

IMT PRECISION ON GLASS

LABORATOIRE NATIONAL DE MÉTROLOGIE ET D'ESSAIS LNE

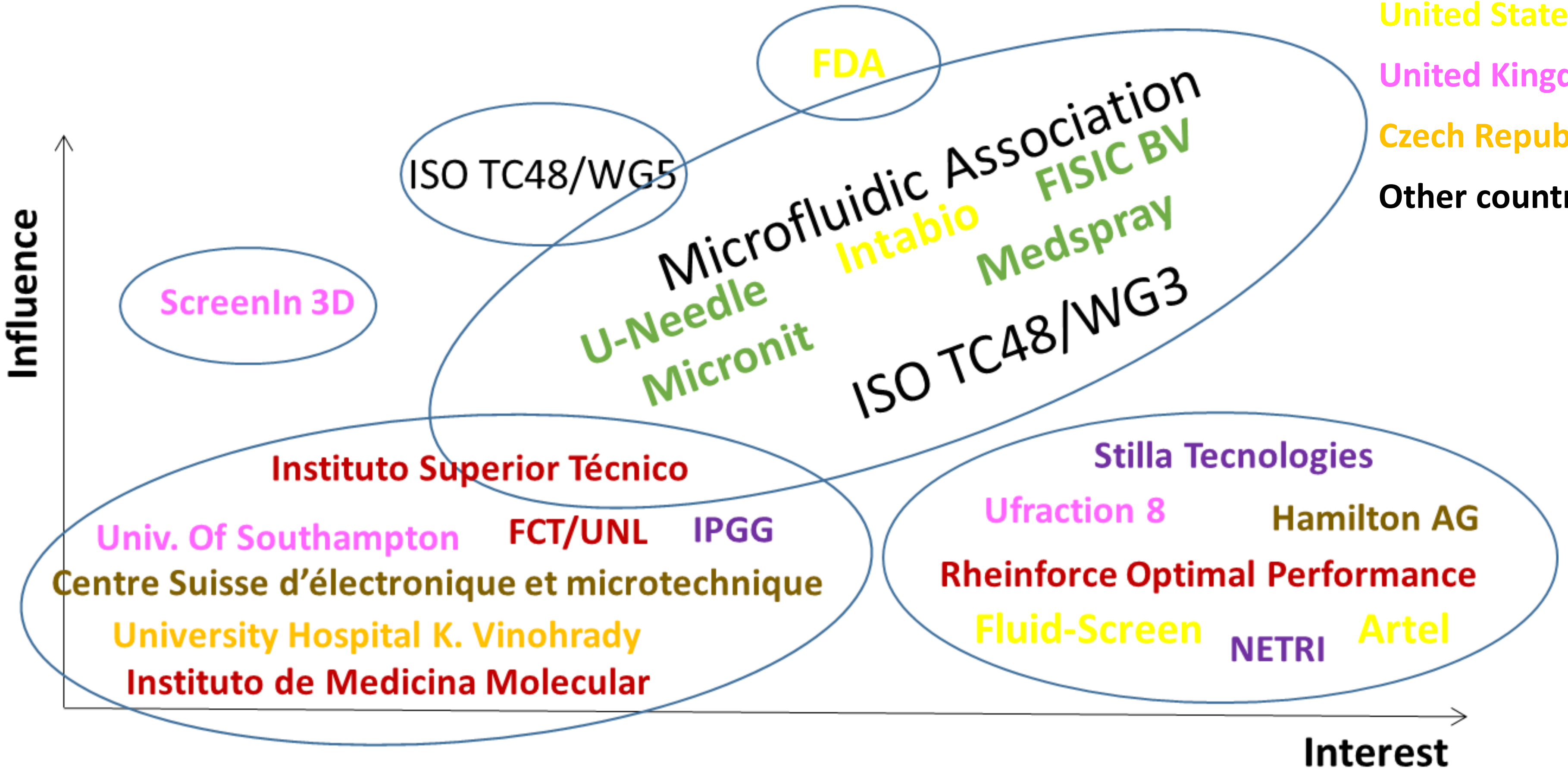
IPQ

TÜBİTAK

INESC MN
Microsystems and Nanotechnologies

ESYP EIM

Stakeholder map 20NRM02 MFMET



The Netherlands

Portugal

Switzerland

France

United States of America

United Kingdom

Czech Republic

Other countries

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Establishing Metrology Standards in Microfluidic Devices

Overview

This project aims <u>to contribute to the development of globally accepted standards for microfluidics</u> and disseminate them to end users in industry (health and pharmaceutical sectors) and academia.

- ✓ by the development of **consensus-based measurement protocols & guidelines**

- ✓ By the **dissemination of metrology standards** towards normative committees (ISO TC48/WG3), industry and end users

Design and manufacture of at least two transfer standards of different material, internal sizes and designs to be tested at metrological quantities

Work Packages Summary

MFMET
Establishing Metrology Standards in Microfluidic Devices

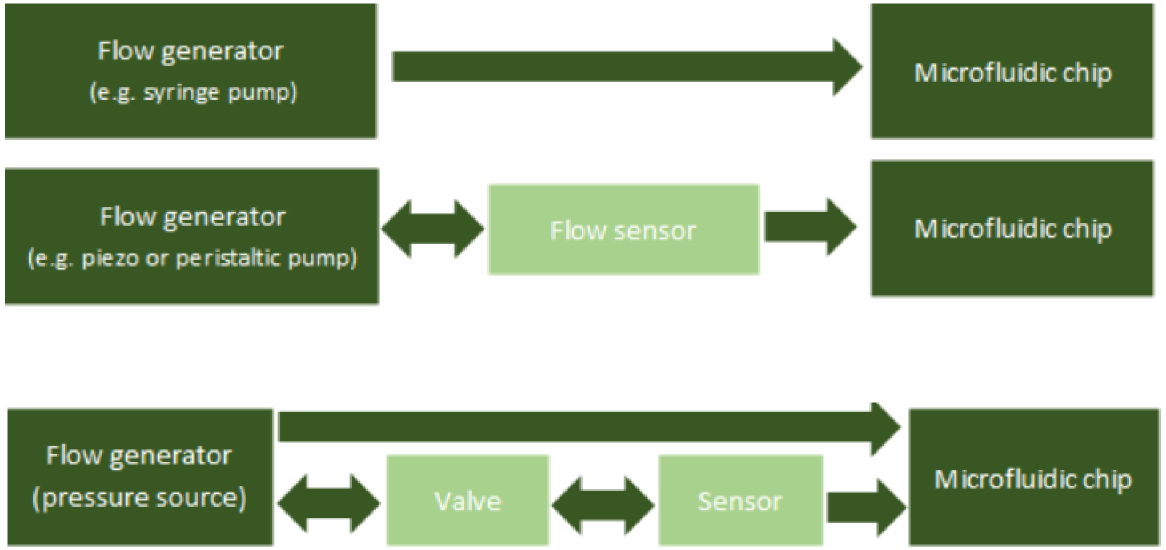
Project Coordinator – Elsa Batista

WP no.	WORK PACKAGE TITLE	WP LEADER	
WP1	Establishment of consensus-based flow control specifications for microfluidics	INESC MN	Vania Silverio
WP2	Development of measurement protocols for microfluidics	CETIAT	Florestan Ogheard
WP3	Development of general standards and guidelines for interfaces and connectivity	IMT	Christina Pecnik
WP4	Development of guidelines for the standardisation of dimensions for modularity and sensor integration	microfluidics ChipShop	Elena Müller
WP5	Creating impact	DTI	Anders Niemann
WP6	Management and coordination	IPQ	Elsa Batista

Major achievements for each WP

WP1 - Consensus-based flow control specifications for microfluidics

- **Literature and Market research**: definitions, characteristics, specifications, application and function of flow control components. Identification of basic and general concepts and associated terms related to flow control.



Type	Supplier	Range		Accuracy
Thermal flow sensors				
LD20-2600B	Sensirion	0 – 1660 µL/min		±0.25 %FSO
Microfluidic flow sensor - MFS	Elveflow	1.5 µL/min - 5 mL/min	down to 1.5 pL/sec	< 5%
µ-FLOW	Bronkhorst	Min: 5 - 100 mg/h Max: 0.1 - 2 g/h		± 2 % FSO
LF6000	Siargo	0.5 - 6.0 mL/min (liquid)	better than 20 µL/min	±3 % or ±0.05 mL/min, which is greater
Differential pressure flow sensor				
MEMS flow meter	Seyonic	1- 200 µL/min		0.5%
Coriolis flow sensor				
Mini CORI-FLOW ML120	Bronkhorst	0.05 - 0.5 g/h, Max 200 g/h		±0.2 % FSO

Major achievements for each WP

Establishing Metrology Standards in Microfluidic Devices

WP1 - Consensus-based flow control specifications for microfluidics

- **Definitions, Symbols and Vocabulary of Flow Control.**
- Generic Specification List for **comparison of flow control components.**

ISO/TC 48

Date: 2022-04-19

ISO/DIS 10991:2022(E)

ISO/TC 48

Microfluidics — Vocabulary

Secretariat: DIN

ISO/DIS 10991
Microfluidics — Vocabulary

General information

Preview

Status : Under development

Edition : 2

Number of pages : 16

Technical Committee : ISO/TC 48 Laboratory equipment

ICS : 01.040.71 Chemical technology (Vocabularies) | 71.040.10 Chemical laboratories. Laboratory equipment

Contents Page

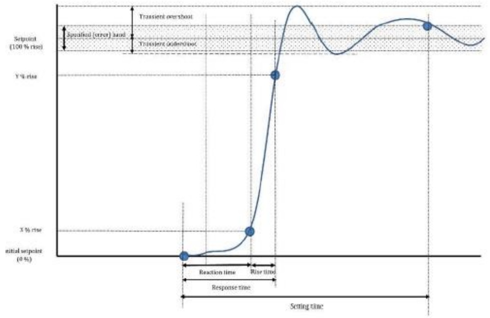


Figure 1 — Schematic showing flow control terms related to a step change in flow

5.1.8
hydrodynamic resistance
ratio of pressure drop over flow rate for a certain component or *system* (3.1.15)

Note 1 to entry: The hydrodynamic resistance is expressed as pressure units per flow rate units.

5.1.9
hydrostatic pressure
pressure that is exerted by a fluid at rest contained within a *system* (3.1.15) due to the force of gravity

Note 1 to entry: The hydrostatic pressure is expressed in pressure units.

5.1.10
internal volume
maximal total available volume comprised within a fluidic component, device or *system* (3.1.15) under normal atmospheric pressure

Note 1 to entry: The internal volume is expressed in volume units such as mm^3 or microliter.

5.1.11
mass flow rate
mass of fluid which passes per unit of time

Note 1 to entry: The mass flow rate is expressed in mass units per time units.

5.1.12
micro pump
miniaturized liquid or gas pumping equipment with *capacity* (4.1.2) of lower than millilitre per minute flow rate

Major achievements for each WP

MFMET
Establishing Metrology Standards in Microfluidic Devices

WP1 - Consensus-based flow control specifications for microfluidics

- **Definitions, Symbols and Vocabulary of Flow Control**.
- Generic Specification List for **comparison of flow control components**.

ISO TC 48

Date: 2022-11

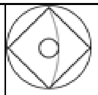
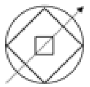
ISO/TS WD 6417(E)

ISO TC 48

Secretariat: DIN

Microfluidic pumps – Symbols and performance communication

Pompes microfluidiques - Symboles et communication des performances

PERISTALTIC PUMP		*Flexible component, alternative directions, peristaltic, flexible, for liquids*
PRESSURE PUMP		*Pneumatic pump, alternative directions, adjustable capacity*
SYRINGE PUMP		*Positive displacement, adjustable capacity, alternative directions*
DIAPHRAGM/MEMBRANE PUMP		*ISO diaphragm pump, flexible*

5.3.2 Requirement of additional consumables

Any requirement for additional consumables, necessary for the correct operation of the pump, should be specified, along with their expected lifetime, dimensions, materials, etc. Examples are removable syringes for syringe pumps, main tubing, fittings and connectors, gaskets, membranes, etc. for peristaltic pumps.

5.3.3 Wetted material

Information about all materials in contact with the fluid should be given in the datasheet. When appropriate, biocompatibility, compatibility with organic solvents, pH-resistance range, temperature and pressure operational ranges of all wetted materials should be provided in the datasheet.

5.3.4 Reversible flow

Information about the possibility of generating and/or handling of flow in alternative directions should be given in the datasheet. If appropriate, a specific duration tolerance for the flow in alternative directions should be given.

ISO/CD TS 6417

Microfluidic pumps — Symbols and performance communication

General information

Status : Under development

Edition : 1

Technical Committee : ISO/TC 48 Laboratory equipment

ICS :

PERISTALTIC PUMP	 *Flexible component, alternative directions, peristaltic, flexible, for liquids*
Scheme	
Description	Successive pinching of a flexible tubing/channel leading to flow movement
Technology characteristics	
Actuation type	
Dead volume	
Requirement of additional consumable	
Tubing size (ID x OD x Length)	
Tubing adaptor	
Reusable	
Wetted material	
Reversible flow	
Closed loop possibility	

Major achievements for each WP

WP1 - Consensus-based flow control specifications for microfluidics

- **Whitepaper on Leakage Testing** – collaboration with The Microfluidics Association.

Microfluidics Association

Version 1 June 1, 2022

Protocols for leakage testing

A Microfluidics Association white paper.

Version 1, June 1, 2022

Henne van Heeren (enablingMNT, the Netherlands)[1], Matthew Davies (Flow Bio, UK), Armelle Keiser (CEA, France), Rudy Lagrauw (Micronit, the Netherlands), Darwin R. Reyes (NIST, USA), Vania Silvero (INESC MN, Portugal), Nicolas Verplanck (CEA, France)

DOI: 10.5281/zenodo.6602162

Overcoming technological barriers in microfluidics: Leakage testing

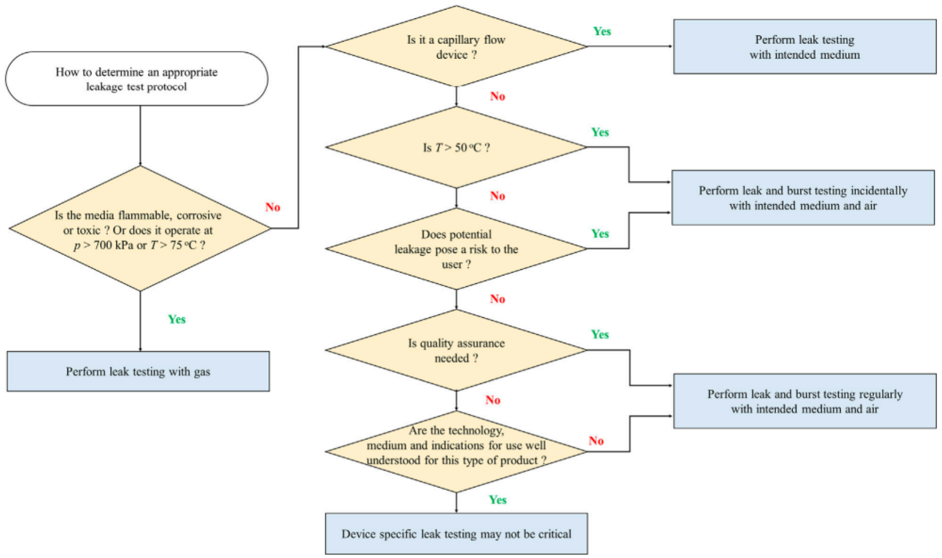
Vania Silverio[1,2], Suvajyoti Guha[3], Armelle Keiser[4], Rucha Natu[3], Darwin R. Reyes[5], Henne van Heeren[6], Nicolas Verplanck[4] and Luke H. Herbertson[3]*

[1]Instituto de Engenharia de Sistemas e Computadores para os Microsistemas e as Nanotecnologias, INESC MN, Lisboa, Portugal, [2]Department of Physics, Instituto Superior Tecnico, Universidade de Lisboa, Lisboa, Portugal, [3]Office of Science and Engineering Laboratories, Center for Devices and Radiological Health, U.S. Food and Drug Administration, Silver Spring, MD, United States, [4]Microfluidic Systems and Bioengineering Lab, Univ. Grenoble Alpes, Technologies for Healthcare and Biology Division, CEA/LETI, Grenoble, France, [5]National Institute of Standards and Technology, Gaithersburg, MD, United States, [6]EnablingMNT/The Microfluidics Association, Dordrecht, Netherlands

Detectable leakage rate [Pa.L/s]: 10^{1}, 10^{0}, 10^{-1}, 10^{-2}, 10^{-3}, 10^{-4}, 10^{-5}, 10^{-6}, 10^{-7}, 10^{-8}, 10^{-9}, 10^{-10}

Method	Measurement	Extent of test: local area	Extent of test: Total area
Dye test	yes	yes	yes
Ultrasonic leak detection	no	yes	no
Bubble test (air / water)	yes	yes	yes
Bubble test (air / foaming solution)	no	yes	no
Pressure decay method	yes	no	yes
Leak tests with tracer gases (NH3, etc.)	yes[1]	yes	yes
Tracer gas method: helium sniffing test	yes[1]	yes	yes

[1] quantification of the leakage rate only conditionally possible in sniffing tests



Major achievements for each WP

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WP2 - Measurement protocols for different flow quantities and liquid properties

- Identification, and **prioritization of quantities and properties** for test protocols of microfluidic devices is concluded.

- A **literature review** of existing metrology and normative standards related to the **flow properties and microfluidic devices** is available on the website.

- A **Metrology Methodology report** is also available on the website.

- Test protocol for **liquid proprieties** measurements completed, Contact angle, Viscosity and Refractive index

- Test protocol on measurement of several **flow quantities completed, Flow, Flow resistivity and Volume.**

- **Development of transfer standards** for flow, volume, material, dimensional and optical quantities.

Major achievements for each WP

WP2 - Measurement protocols for different flow quantities and liquid properties

- A **Metrology Methodology report** is available on the website.

Establishing Metrology Standards in Microfluidic Devices

REPORT:

A2.1.1: Metrology Methodology

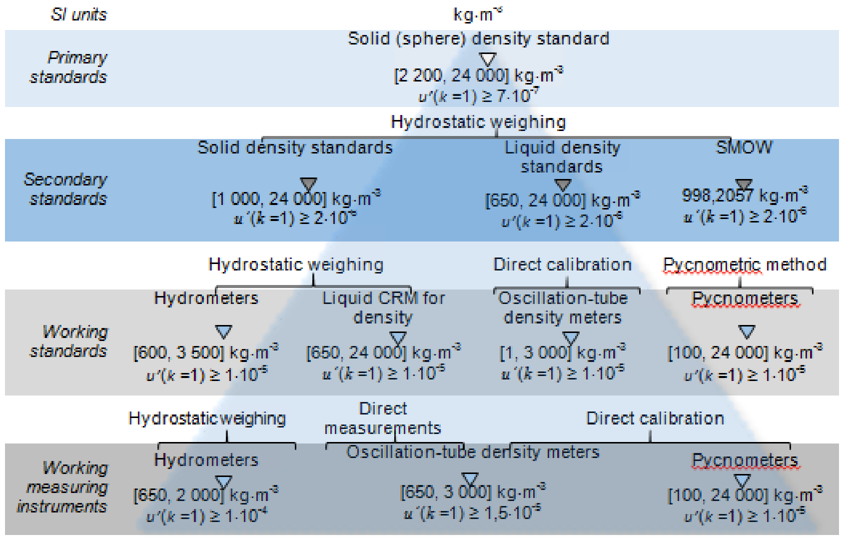
Work package 2

Contents

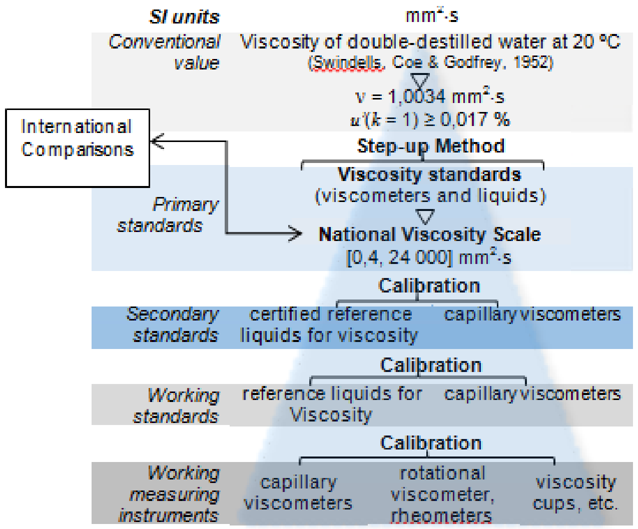
Major achievements for each WP

WP2 - Measurement protocols for different flow quantities and liquid properties

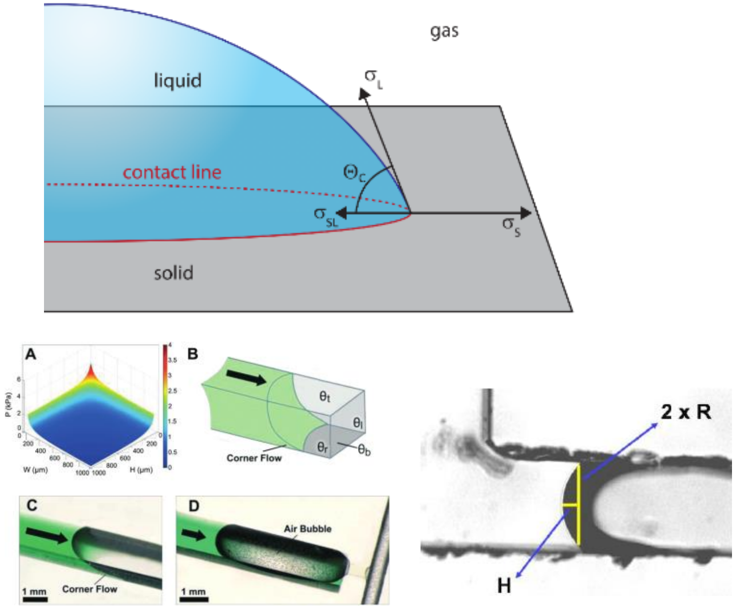
- Test protocol for **liquid proprieties** measurements, Density, Contact angle, Viscosity and Refractive index



Density traceability chain



Viscosity traceability chain



Contact angle on a surface and in a channel

Major achievements for each WP

Establishing Metrology Standards in Microfluidic Devices

WP2 - Measurement protocols for different flow quantities and liquid properties

- Test protocol for **flow proprieties** measurements, flow, flow resistivity, and volume:

Establishing Metrology Standards in Microfluidic Devices

REPORT:

A2.2.2: Development of test protocols for microfluidic devices

Work package 2

- one pressure sensor at the device's inlet, the outlet being at atmospheric pressure, as shown in the following schematic:

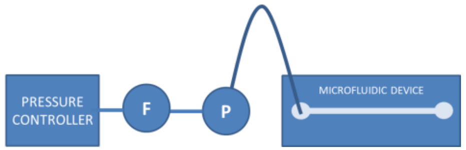


Figure 1: One pressure sensor

- one differential pressure sensor in parallel of the microfluidic device, as shown in the following schematic:

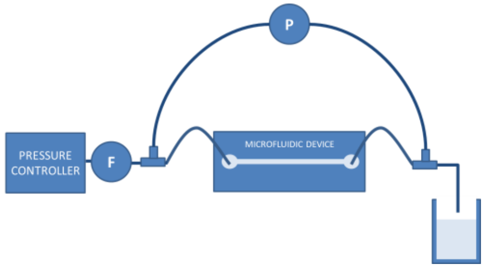
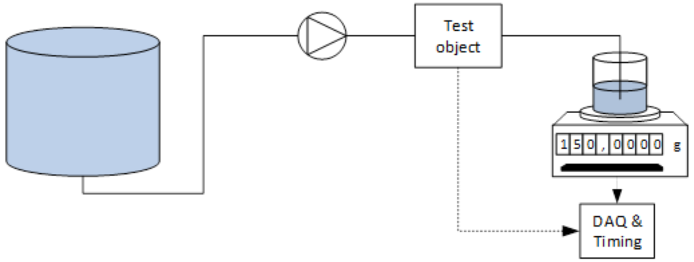
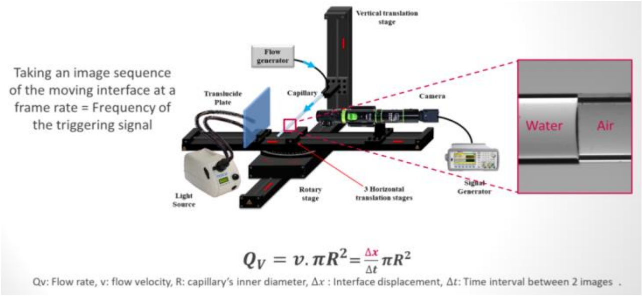


Figure 2: One differential sensor

- two pressure sensors at inlet and outlet of the microfluidic device, as shown in the following schematic:

Flow resistivity test methods





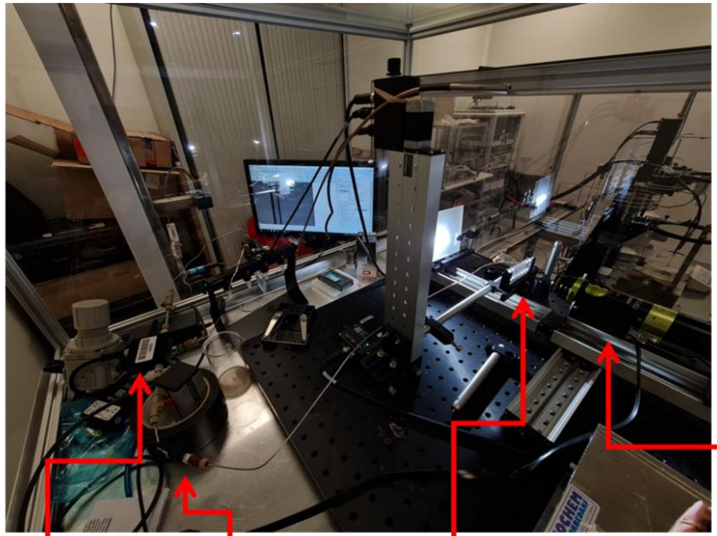
Micro and nano flow test methods

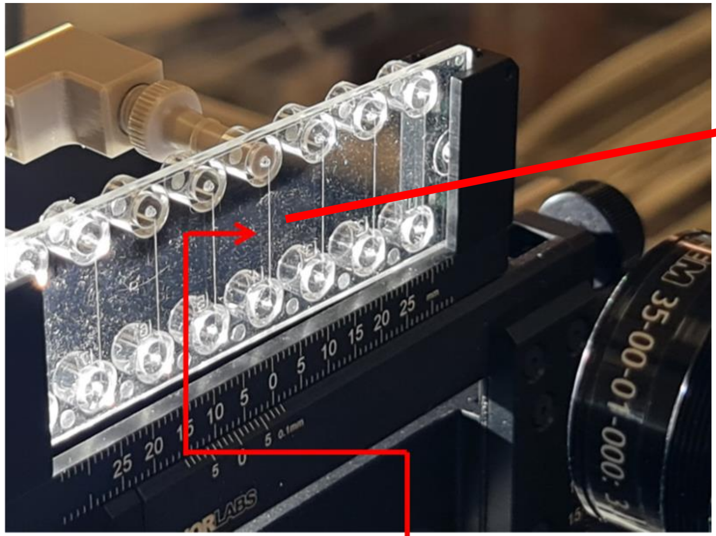
Major achievements for each WP

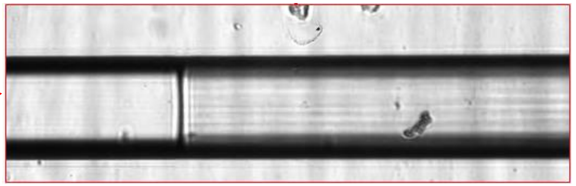
Establishing Metrology Standards in Microfluidic Devices

WP2 - Measurement protocols for different flow quantities and liquid properties

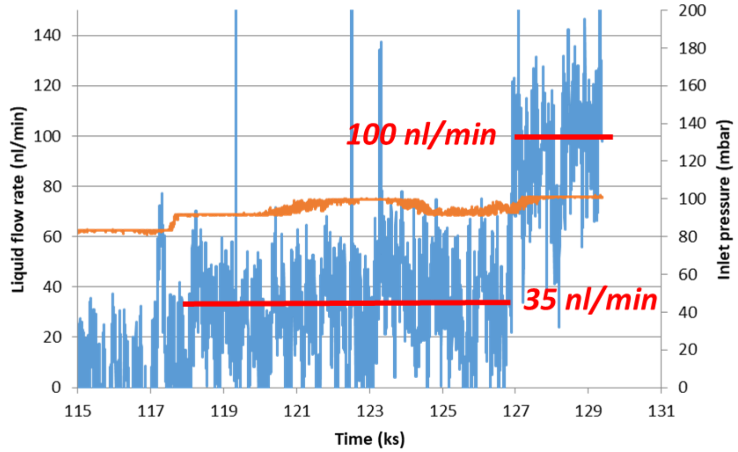
- Application of test protocol for **flow proprieties** measurements, flow, flow resistivity, and volume:





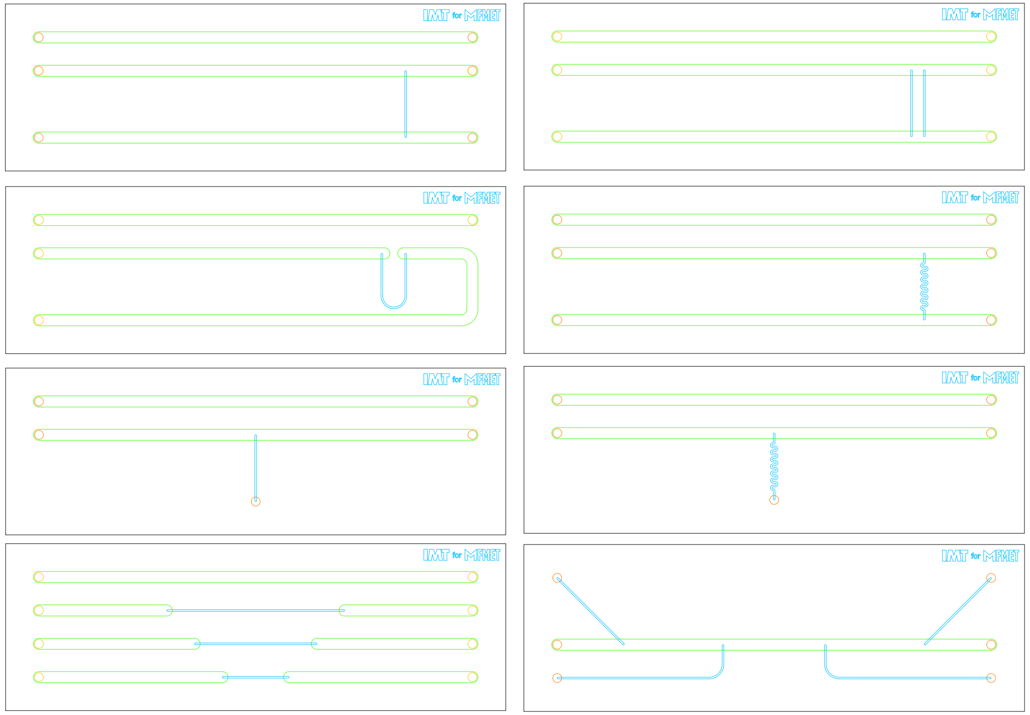



Flow and pressure measurements in "Systema D" chip channel n°4



Major achievements for each WP

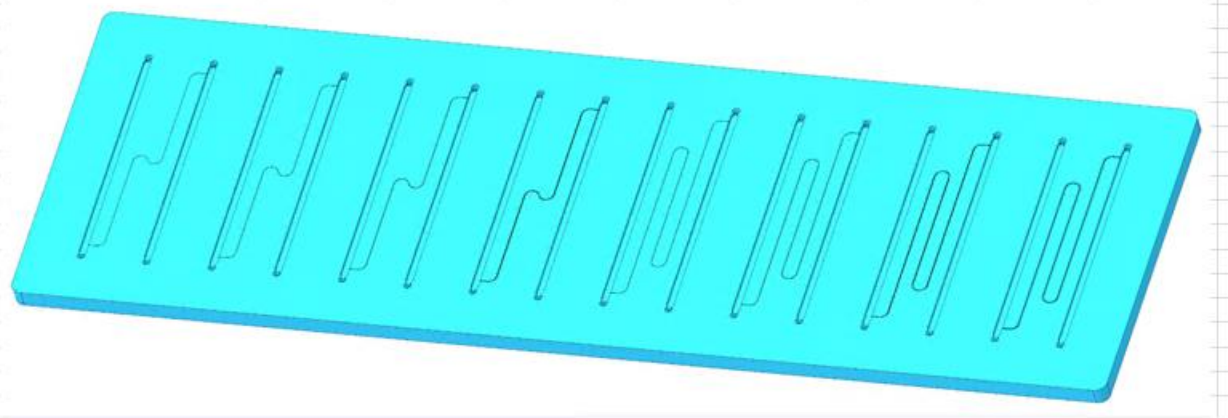
WP2 – Glass & polymer transfer standards (microfluidic chips)



Glass standard designs

MFMET polymer golden standards design (MFCS design proposal)

Design n°	1	2	3	4	5	6	7	8
Height (µm)	5	10	20	50	10	20	50	100
Width (µm)	5	10	20	50	10	20	50	100
Length (mm)	20	20	20	20	40	40	40	40
Flow at 100 mbar inlet (µl/min)	0.00066	0.01	0.17	6.6	0.00528	0.08	3.3	52.82
Flow at 2 bar inlet (µl/min)	0.01	0.21	3.38	132.04	0.11	1.69	66.02	1060



Polymer standard designs

These transfer standard are designs to be used **to disseminate traceability** on flow, flow resistivity, volume, channels dimensions, roughness to microfluidics manufacturers and end-users, and **will be characterized by NMIs** for those quantities.

Major achievements for each WP

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Establishing Metrology Standards in Microfluidic Devices

WP3 - General standards and guidelines for interfaces and connectivity

- Based on survey results, investigation of suppliers of microfluidic components and discussions with experts conducted by EnablingMNT, partners could **identify** the most important and commonly **used materials for microfluidics**:
    - COC/COP for microfluidic chips/substrates and several other applications,
    - glass for microfluidic chips/substrates,
    - PEEK and PFTE for connectors, tubes, pumps etc. and
    - PC for cell cultures / organ on chip

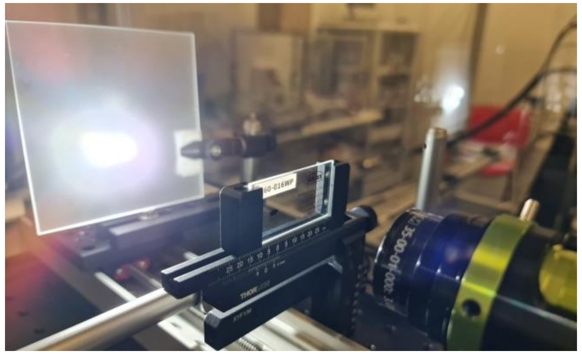
- A Test protocol for **hydrophobicity, hydrophilicity and wettability** was concluded.

Major achievements for each WP

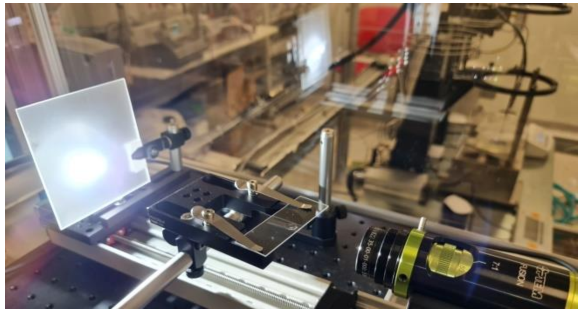
Establishing Metrology Standards in Microfluidic Devices

WP3 - General standards and guidelines for interfaces and connectivity

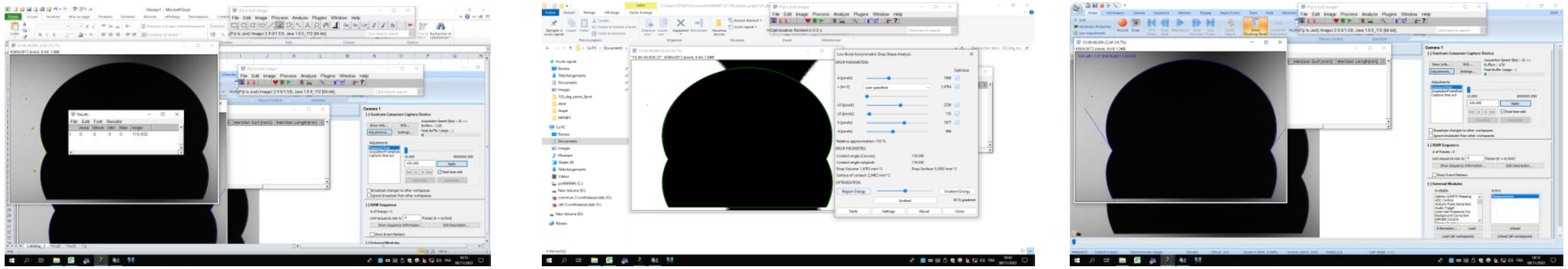
- Application of contact angle test protocol and calculation of surface energy (quantifying wettability) at CETIAT Liquid flow laboratory:



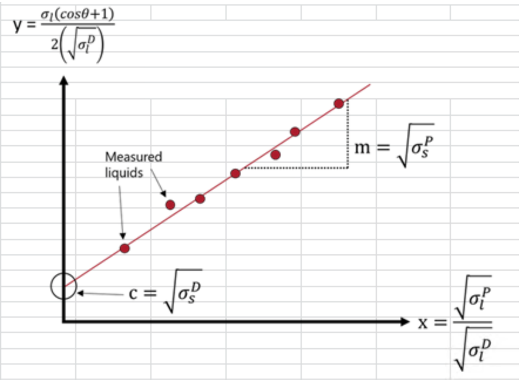
Calibration using an angle standard



Measurement of contact angle

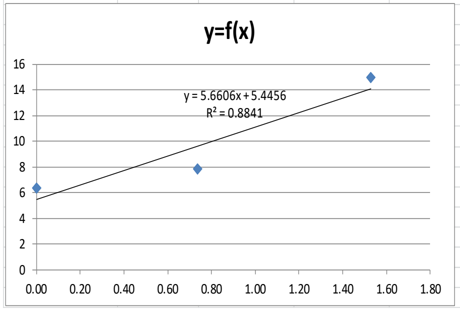


Comparison of 3 contact angle measurements algorithm using ImageJ software



Use of OWRK Model for the calculation of surface energy using 3 contact angle measurements
Of ultrapure water, ethylene glycol and diiodomethane

test liquid	theta	cos(theta)	sig d l	sig p l	sig l	y	x
water	22.93	0.92	21.8	51	72.8	14.98	1.53
diiodomethane	37.71	0.79	50.8	0	50.8	6.38	0.00
ethylene glycol	34.89	0.82	30.9	16.8	47.7	7.81	0.74



m	5.66		
m^2	32.04	mN/m	(sig P S)
c	5.45		
c^2	29.65	mN/m	(sig D S)

Surface energy (sig s) = 61.70 mN/m

WP5 - Impact

- 2 **Papers** published

  - *Metrology challenges for microfluidics*, CMM International, in April 2022

  - *Overcoming Technological Barriers in Microfluidics*: Leakage Testing. Frontiers in Bioengineering and Biotechnology, 10: 958582, https://doi.org/10.3389/fbioe.2022.958582

- 2 **Whitepaper** published in collaboration with The MFA, **one on Leakage Testing and** onother **on hydrophobicity, hydrophilicity, and wettability**

- 2 **Poster presentations**

  - *A new EURAMET EMPIR Project: establishing metrology standards in microfluidic devices,* CIM2021, September 2021

  - *Influence of Microfluidic Standards in Organs-on-Chips,* EUROOCs, July 2022

- 3 **Oral Presentations**

  - *The road to user friendly integration of microfluidic components and devices,* The Microfluidics Association Webinar, May 2022

  - *Metrology Challenges,* Polymer Replication Nanoscale Conference, May 2022

  - What can microfluidics standardization do for you? IVAM Microfluidics, October 2022

WP5 - Standardization

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- **ISO/TC48/WG3 - Microfluidic devices**
  - Comments sent on:
    - ISO 22916 : Microfluidic devices — Interoperability requirements for dimensions, connections and initial device classification
    - ISO/DIS10991 : Microfluidics - Vocabulary
  - Active participation in ISO TS WD 6417-Microfluidic pumps – Symbols and performance communication development.
- **TC48/WG5-Liquid handling devices- automatic**
  - Active participation mainly for the development of ISO/TR 6037 - Automated liquid handling systems – Uncertainty of the measurement procedures.
- **New CEN FG OOC – Organ-on-Chip**
  - Active participation in the development of the scope and WG (working groups).

Conclusions

MFMET
Establishing Metrology Standards in Microfluidic Devices

- Presentation of the objectives and initial outcomes of EMPIR Project **20NRM02 MFMET - Establishing metrology standards in microfluidic devices**.
  - This project intends to tackle the lack of metrological specifications for microfluidics, which are now being addressed in technical WP1 to WP4

- Reports and test protocols developped (experimental validation ongoing) for:
  - Leakage and burst pressure
  - Flow, flow resistivity and volume
  - Density, viscosity, refractive index and contact angle, and more to come

- Transfer standards available in 2024 to disseminate traceability in microfluidics!

The Team

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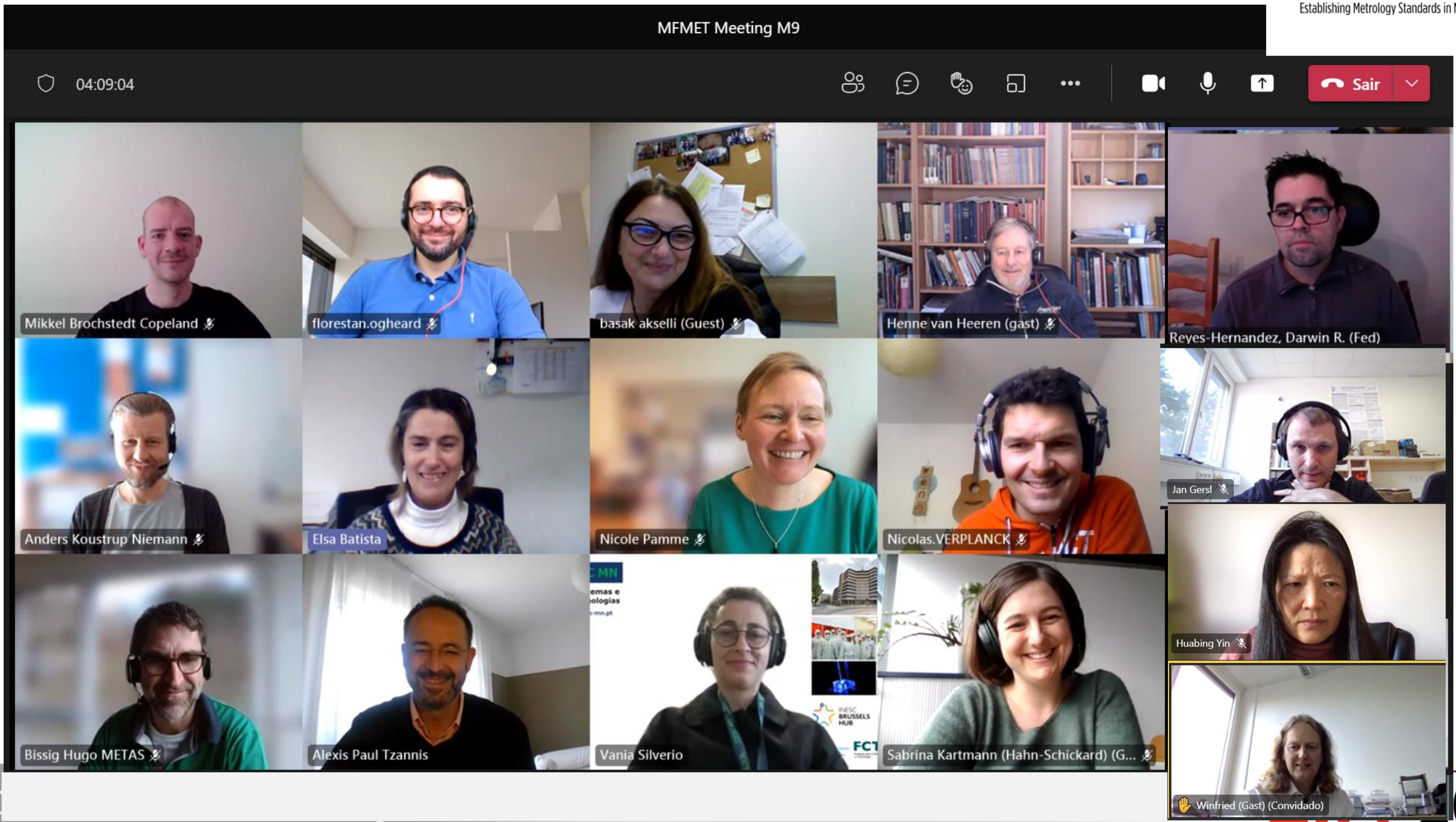
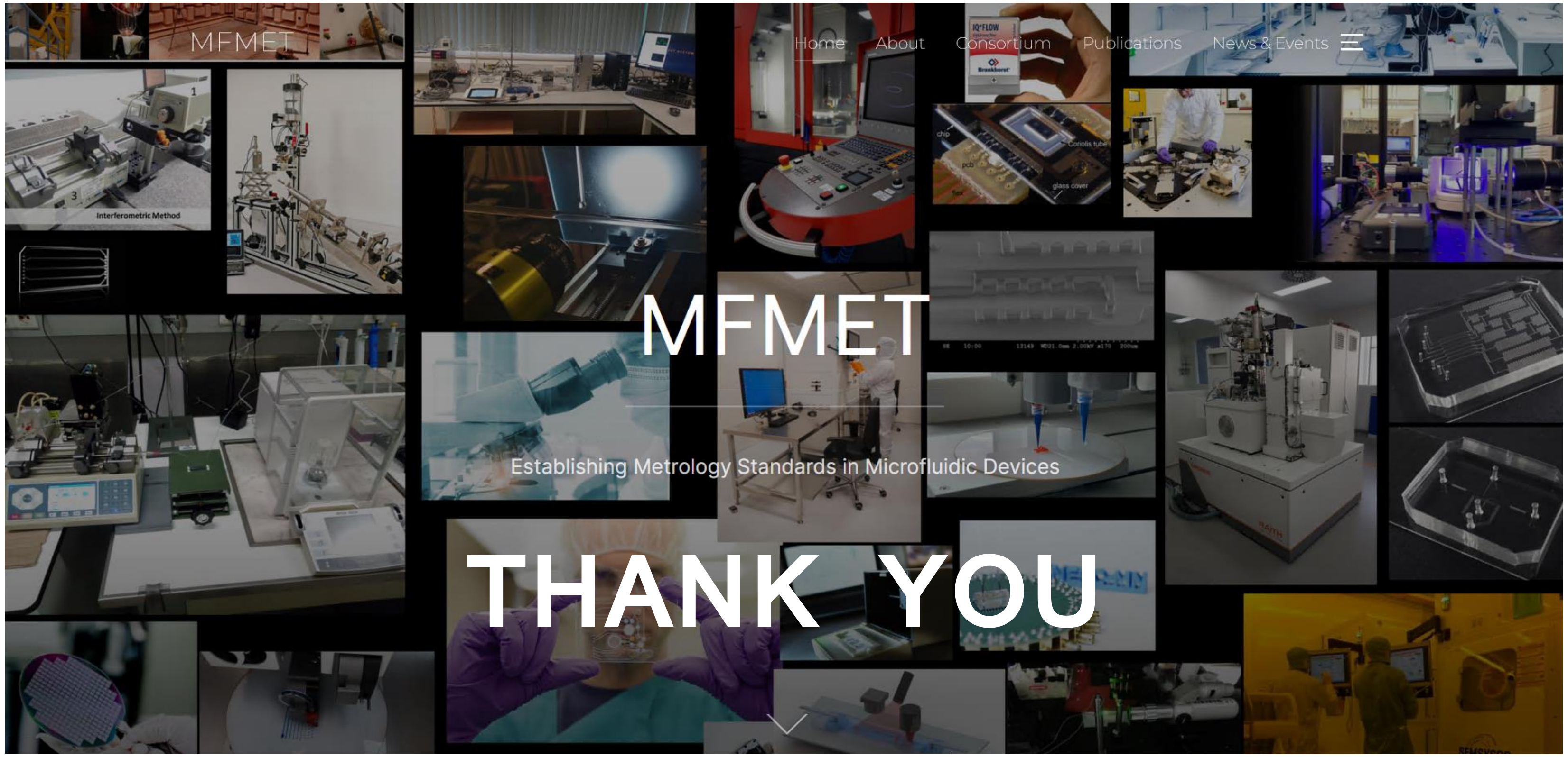
Establishing Metrology Standards in Microfluidic Devices



https://mfmet.eu

https://zenodo.org/communities/mfmet



MFMET

Establishing Metrology Standards in Microfluidic Devices

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EMPIR EURAMET

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