METROLOGY for DRUG DELIVERY

MEDD II
Drugmetrology.com

Wokshop on microflow calibration methods:

Optical Methods

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***Abir Wissam Boudaoud**, PhD Student, abir-wissam.boudaoud@cetiat.fr*

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ensemble, innover et valider

18th Nov. 2020

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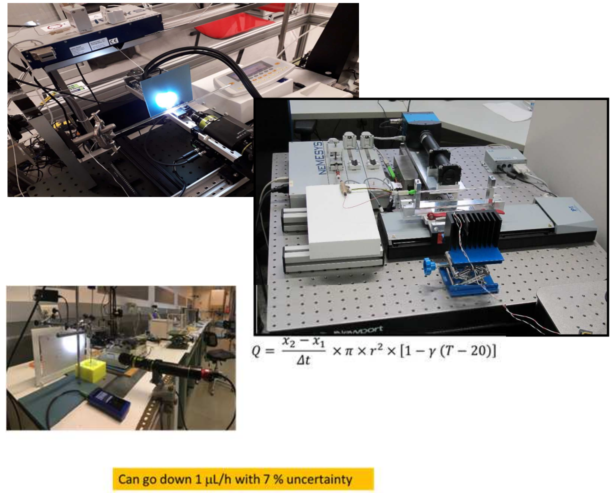
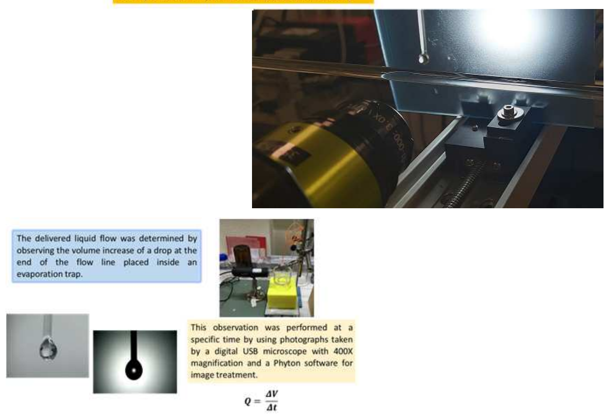
Overview

1. Interface tracking method
   - ➢ Principle (example at CETIAT)
   - ➢ Uncertainty budget (example at CETIAT)
   - ➢ IPQ & THL Interface Tracking Setups



2. Pendant drop method
   - ➢ Principle (example at CETIAT)
   - ➢ IPQ Pendant Drop setup



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Optical nano-flow standards

- Micro-flow = 1 ml/h (16 µl/min) to 1 L/h (16 ml/min)
  1 drop/ minute to 5 drop/ second

- Nano-flow = ~1 µl/h (16 nl/min) to 1 ml/h (16 µl/min)
  1 drop/ month to 1 drop / minute

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Optical nano-flow standards: applications

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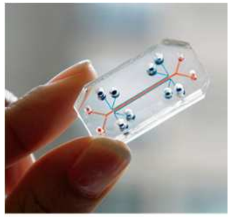
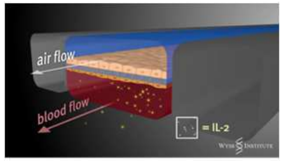
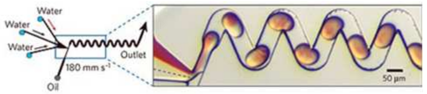


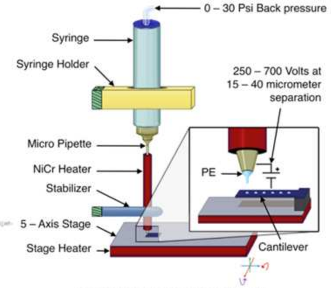




DeMello, Andrew. (2006). Control and detection of chemical reactions in microfluidic systems. Nature. 442. 394-402. 10.1038/nature05062.

Microfluidics: Digital Microfluidics and Organs-on-chip

Electrohydro-dynamic Ink Jet Printing

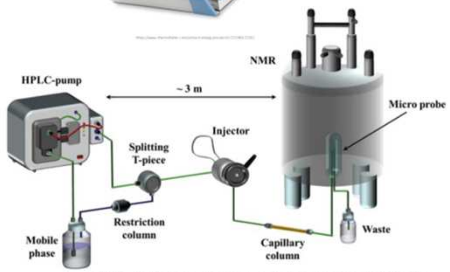


Nano-Flow Rates

Continuous Dosing of Laboratory Animals

etc,...

Nano-Liquid Chromatography



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Optical nano-flow standards: applications

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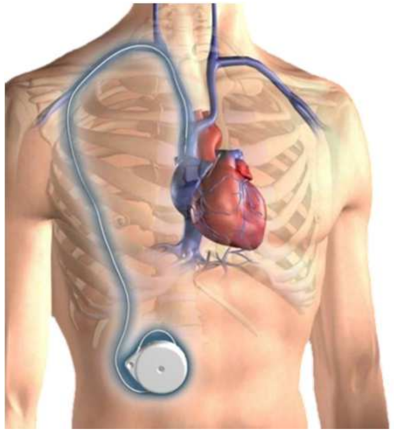
Implantable Infusion Pumps



https://docplayer.net/82396718-United-therapeutics-corporation.html

https://www.medtronic.com/us-en/healthcare-professionals/products/neurological/drug-infusion-systems/synchromed-ii.html

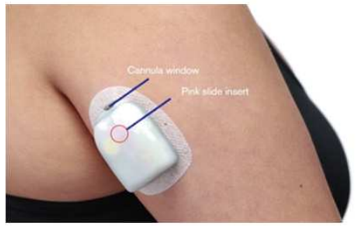
https://bmccancer.biomedcentral.com/articles/10.1186/s12885-019-5515-6/figures/2

Flow rates range : 0,048 ml/day → 3 ml/day

$Q_{L\ min}$= 33 nl/min

Insulin Pumps

https://myglu.org/articles/sales-of-medtronic-paradigm-pump-line-discontinued



https://www.omnipod.com/fr-ch/educational-resources/videos

https://www.medtronic-diabetes.co.uk/insulin-pump-therapy/minimed-640g-system

Basal rate: 0,02 U/h → 50 U/h

$Q_{L\ min}$= 3 nl/min

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Optical nano-flow standards: applications

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Implantable Infusion Pumps

Insulin Pumps

https://docplayer.net/8239671

Need to be calibrated against primary standards to ensure the traceability of measurements to the I.S. of Units!

https://www.medtronic-diabetes.co.uk/insulin-pump-therapy/minimed-640g-system

Flow rates range : 0,048 ml/day → 3 ml/day
$Q_{L\ min}$= 33 nl/min

Basal rate: 0,02 U/h → 50 U/h
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Optical nano-flow standards: MeDDII project

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➔ To develop primary standards down to 5 nl/min with expanded uncertainty of 2% (k=2)

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Microflow standards (MeDD I)

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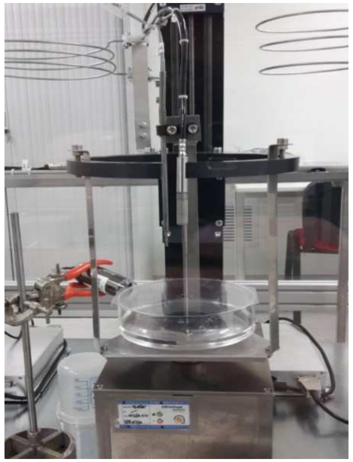
cofrac ETALONNAGE ACCREDITATION N° 2-57 DEBIMETRIE LIQUIDE PORTÉE disponible sur www.cofrac.fr

CETIAT's micro-flow bench

Gravimetric Method



$$Q = \frac{\Delta m}{\Delta t}$$

The laboratory of liquid flow and micro-liquid flow measurement is COFRAC accredited for flow rates going down to 16µL/min with best U(k=2) = 0.1%

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Optical nano-flow standards at CETIAT

- Ongoing PhD Thesis collaboration
- PhD student: **Abir Wissam Boudaoud**

Florestan OGHEARD

Teresa LOPEZ-LEON and Joshua D. McGraw

➔Development of a primary standard for nano-flow rates of liquids

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Interface Tracking: principle at CETIAT

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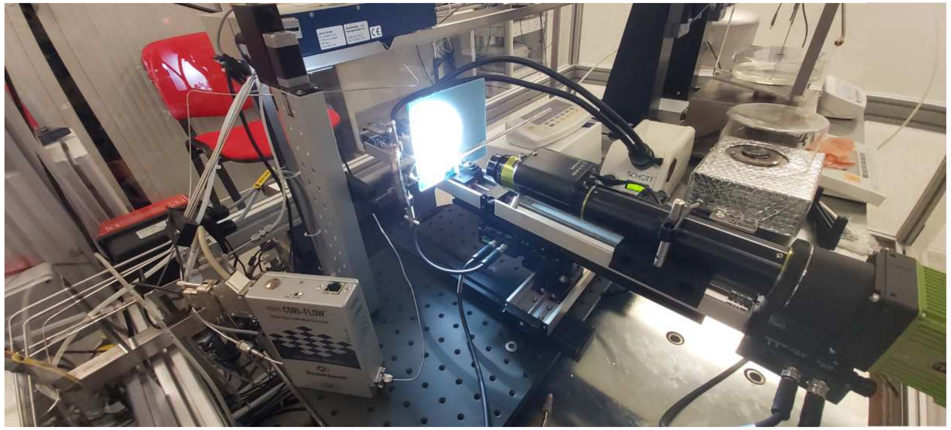
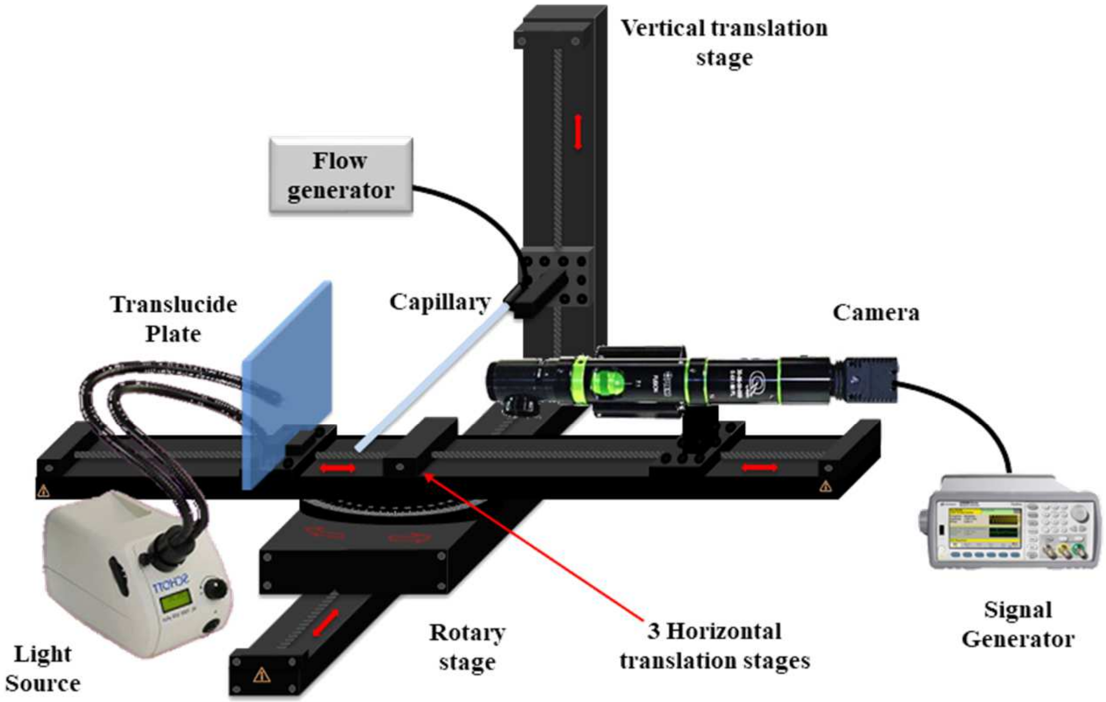


CETIAT's Interface Tracking calibration system



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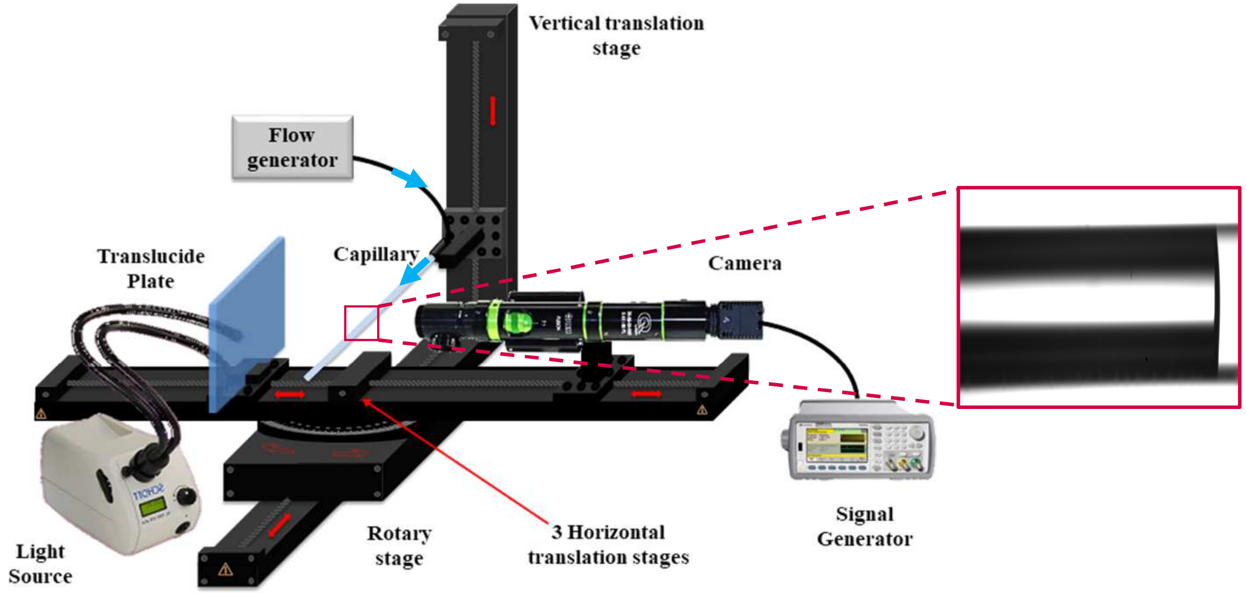
Interface Tracking: principle at CETIAT

1. Generation of a liquid flow

2. Image acquisition of the liquid/air interface once this one enters in the camera‘s field of view

3. Measurement of the interface’s displacement by image processing



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Interface Tracking: principle at CETIAT

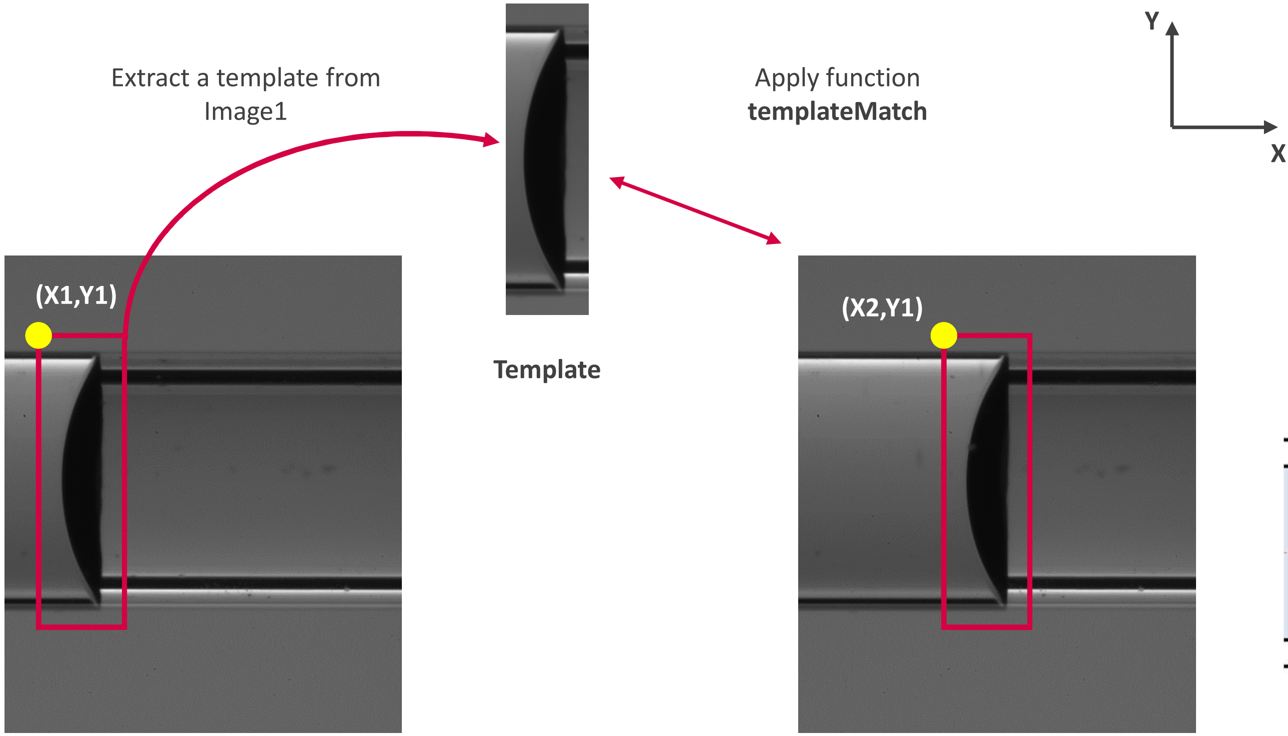
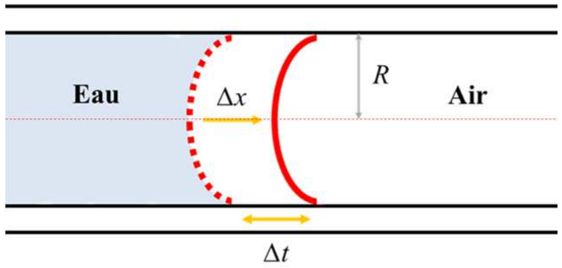


Image1 (t1)

Image2 (t2)

$$\Delta X(t1, t2) = X2 - X1$$



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Interface Tracking: principle at CETIAT

Extract a template from Image1

Apply function **templateMatch**

Y

X

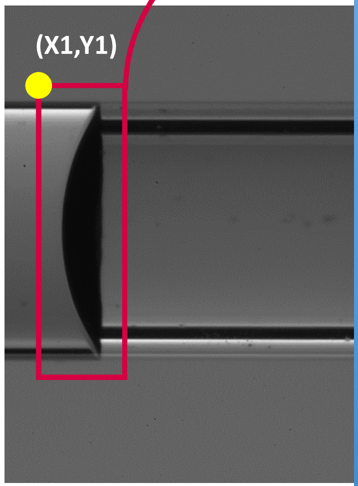

Image1 (t1)

$$) = X2 - X1$$

$$Q_V = v.\pi R^2 = \frac{dx}{dt}.\frac{\pi}{4}d^2$$

Qv: Flow rate, v: Flow velocity,

R: Capillary's inner radius, d: Capillary's inner diameter, x: Interface positions, t: time

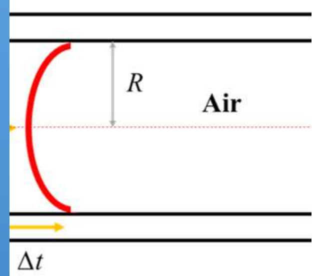

Image2 (t2)

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Interface Tracking: principle at CETIAT
Uncertainty Budget

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Flow rate : $Q_V = v.\pi R^2 = \frac{x}{t}.\frac{\pi}{4}R^2$

Measurement uncertainty : $u(Q_V) = \sqrt{\left(\frac{\partial Q_v}{\partial d}\right)^2.u^2(d) + \left(\frac{\partial Q_v}{\partial x}\right)^2.u^2(x) + \left(\frac{\partial Q_v}{\partial t}\right)^2.u^2(t)}$

diameter

Camera resolution	
Camera calibration	Objective micrometer
	Position in the focal plane
	Position in the field of view
Intensity profile	
Drift	
Temperature effect	

displacement

Camera resolution	
Camera calibration	Objective micrometer
	Position in the focal plane
	Position in the field of view
Correlation function	
Motion blur	
Motion plane angle	

time

Calibration of the signal generator
Exposure time
Drift
Temperature effect

+

Linear fit residus from x=f(t)
Thermal expansion
Evaporation

For 5 nl/min :

$U(Q_{ref})$ = 11 % (k=2) for a 1 second measurement at 5 fps
$U(Q_{ref})$ = 0.5 % (k=2) for a 120 seconds measurement at 5 fps

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diameter

Camera resolution	
Camera calibration	Objective micrometer
	Position in the focal plane
	Position in the field of view
Intensity profile	
Drift	
Temperature effect	

displacement

Camera resolution	
Camera calibration	Objective micrometer
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Motion plane angle	

time

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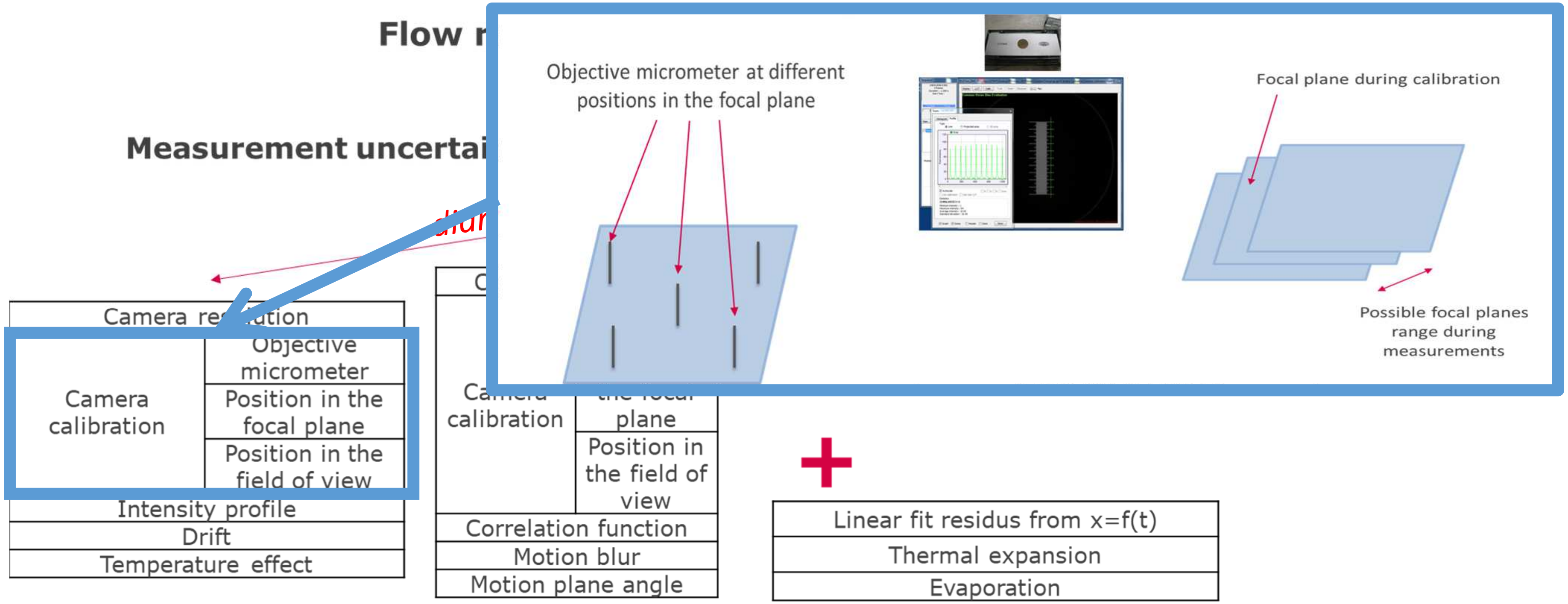
Interface Tracking: principle at CETIAT Uncertainty Budget



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Interface Tracking: principle at CETIAT
Uncertainty Budget

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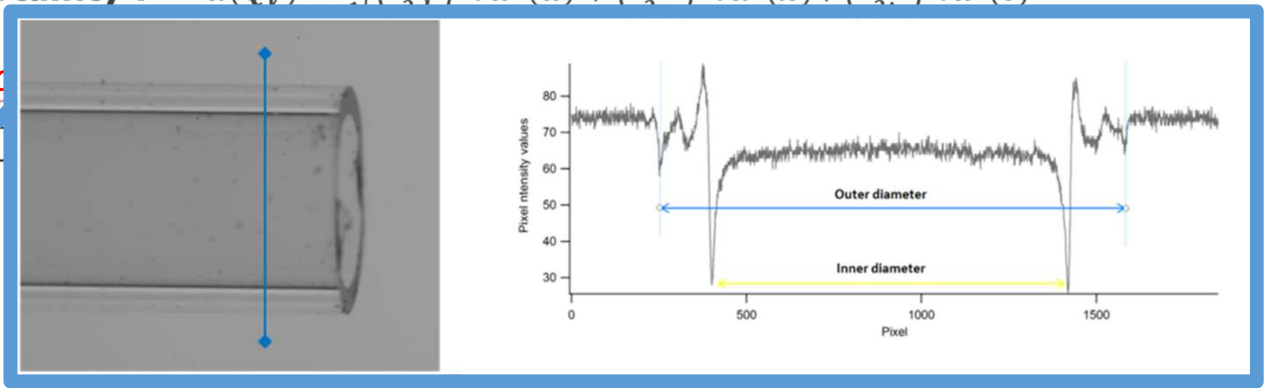
Measurement uncertainty : $$u(Q_V) = \sqrt{\left(\frac{\partial Q_v}{\partial d}\right)^2 .u^2(d) + \left(\frac{\partial Q_v}{\partial x}\right)^2 .u^2(x) + \left(\frac{\partial Q_v}{\partial t}\right)^2 .u^2(t)}$$

Camera resolution	
Camera calibration	Objective micrometer
	Position in the focal plane
	Position in the field of view
Intensity profile	
Drift	
Temperature effect	

	view
Correlation function	
Motion blur	
Motion plane angle	

Linear fit residus from x=f(t)
Thermal expansion
Evaporation



For 5 nl/min :

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Interface Tracking: principle at CETIAT
Uncertainty Budget

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Flow rate : $Q_V = v.\pi R^2 = \frac{x}{t}.\frac{\pi}{4}R^2$

Measurement uncertainty :

EVALUATED BY SUCCESSIVE CALIBRATIONS AND AT DIFFERENT TEMPERATURES

diameter

Camera resolution	
Camera calibration	Objective micrometer
	Position in the focal plane
	Position in the field of view
Intensity profile	
Drift	
Temperature effect	

displac

Camera resolution	
Camera calibration	Objective micrometer
	Position in the focal plane
	Position in the field of view
Correlation function	
Motion blur	
Motion plane angle	

Calibration of the signal generator
Exposure time
Drift
Temperature effect

\+

Linear fit residus from x=f(t)
Thermal expansion
Evaporation

For 5 nl/min :

$U(Q_{ref})$ = 11 % (k=2) for a 1 second measurement at 5 fps
$U(Q_{ref})$ = 0.5 % (k=2) for a 120 seconds measurement at 5 fps

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Interface Tracking: principle at CETIAT
Uncertainty Budget

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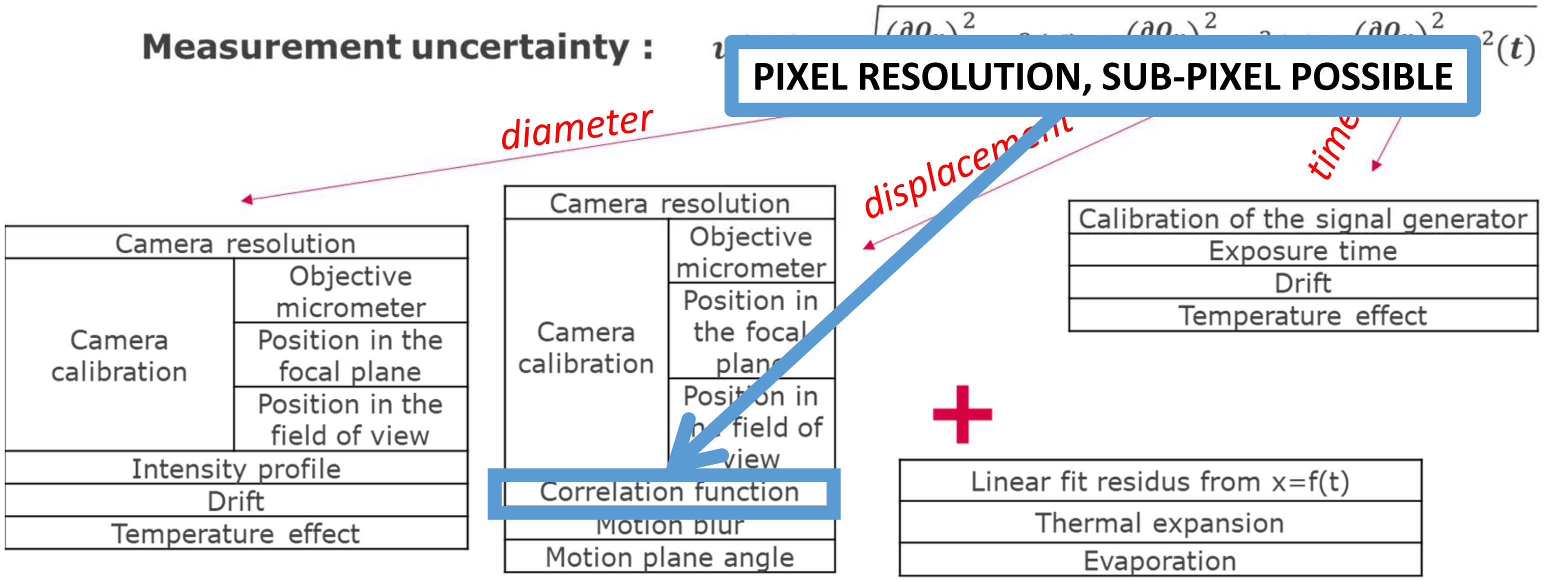
Flow rate : $Q_V = v.\pi R^2 = \frac{x}{t} . \frac{\pi}{4} R^2$



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Interface Tracking: principle at CETIAT
Uncertainty Budget

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Flow rate : $Q_V = v.\pi R^2 = \frac{x}{t}.\frac{\pi}{4}R^2$

Measurement uncertainty : $u($…

Distance D travelled by the interface during exposure time:

$$D = v.t_{exposure}$$

V: Interface displacement velocity

$t_{exposure}$: exposure time

diameter

Camera resolution		
Camera calibration	Objective micrometer	
	Position in the focal plane	
	Position in the field of view	
Intensity profile		
Drift		
Temperature effect		

Camera resolut…		
Camera calibration	Obje… micrometer	
	Position in the focal plane	
	Position in the field of view	
Correlation function		
Motion blur		
Motion plane angle		

Exposure time
Drift
Temperature effect

\+

Linear fit residus from x=f(t)
Thermal expansion
Evaporation

For 5 nl/min :

$U(Q_{ref})$ = 11 % (k=2) for a 1 second measurement at 5 fps

$U(Q_{ref})$ = 0.5 % (k=2) for a 120 seconds measurement at 5 fps

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Interface Tracking: principle at CETIAT Uncertainty Budget

Flow rate : $Q_V = v.\pi R^2 = \frac{x}{t}.\frac{\pi}{4}R^2$

Measurement uncertainty : $u($

Distance D travelled by the interface during exposure time:

$$D = v.t_{exposure}$$

V: Interface displacement velocity

$t_{exposure}$: exposure time

diameter

Camera resolution		
Camera calibration	Objective micrometer	
	Position in the focal plane	
	Position in the field of view	
Intensity profile		
Drift		
Temperature effect		

Camera resolut		
Camera calibration	Obje micrometer	
	Position in the focal plane	
	Position in the field of view	
Correlation function		
Motion blur		
Motion plane angle		

Exposure time
Drift
Temperature effect

\+

Linear fit residus from x=f(t)
Thermal expansion
Evaporation

For 5 nl/min :

$U(Q_{ref})$ = 11 % (k=2) for a 1 second measurement at 5 fps
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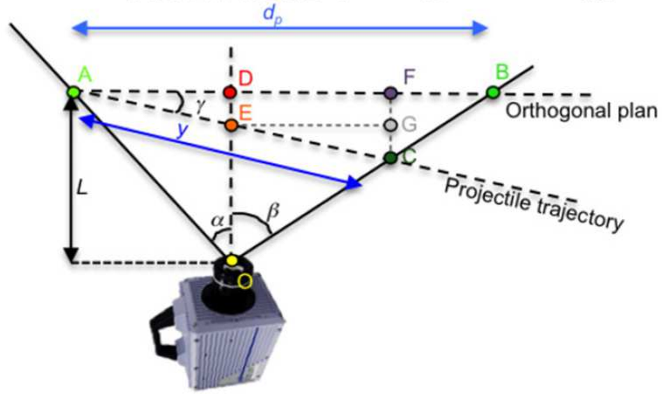
Interface Tracking: principle at CETIAT Uncertainty Budget

Meas



$$y = \frac{d_p}{\cos\gamma + \tan\beta \sin\gamma}.$$

https://www.metrology-journal.org/articles/ijmqe/abs/2014/02/ijmqe140007/ijmqe140007.html

Camera re	
Camera calibration	field of view
Intensity profile	
Drift	
Temperature effect	

	the fie… of view
Correlation function	
Motion blur	
Motion plane angle	

Linear fit residus from x=f(t)
Thermal expansion
Evaporation

For 5 nl/min :

$U(Q_{ref})$ = 11 % (k=2) for a 1 second measurement at 5 fps
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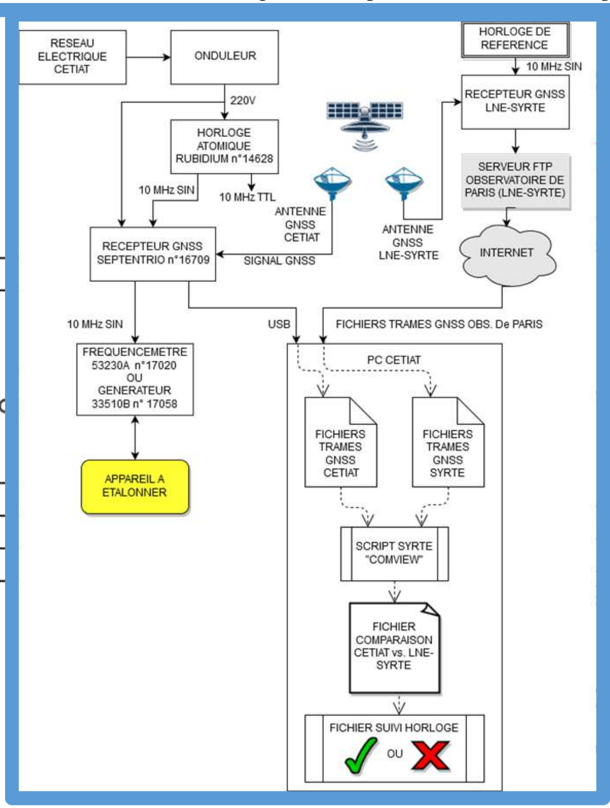
Interface Tracking: principle at CETIAT
Uncertainty Budget

CETIAT's Time & Frequency Traceability Chain



$$\ldots R^2 = \frac{x}{t}.\frac{\pi}{4}R^2$$

$$u(Q_V) = \sqrt{\left(\frac{\partial Q_v}{\partial d}\right)^2.u^2(d) + \left(\frac{\partial Q_v}{\partial x}\right)^2.u^2(x) + \left(\frac{\partial Q_v}{\partial t}\right)^2.u^2(t)}$$

displacement

time

...esolution
Objective micrometer
Position in the focal plane
Position in the field of view
...n function
...n blur
...ane angle

Calibration of the signal generator
Exposure time
Drift
Temperature effect

+

Linear fit residus from x=f(t)
Thermal expansion
Evaporation

For 5 nl/min :

...r a 1 second measurement at 5 fps

...or a 120 seconds measurement at 5 fps

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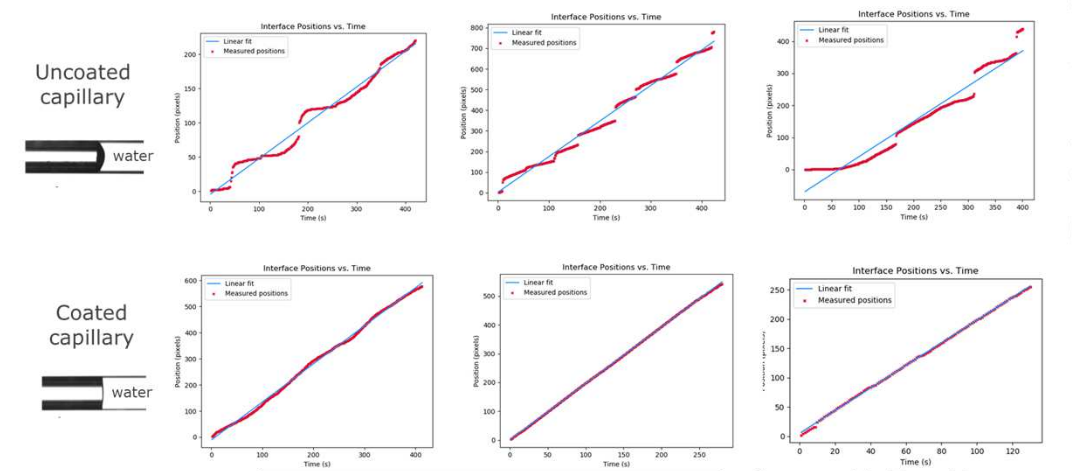
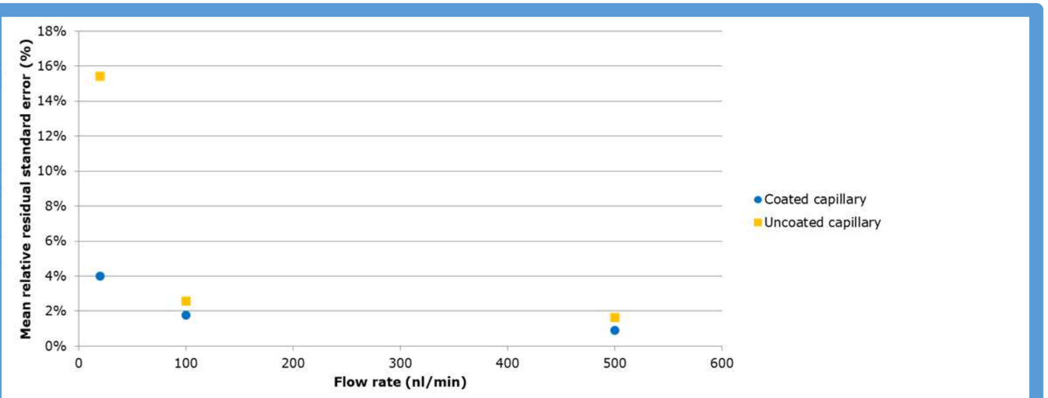
Interface Tracking: principle at CETIAT
Uncertainty Budget

Slip & Stick Effect





Mean linear fits residuals in the coated (blue) and uncoated (orange) cases

Temperature effect

Motion plane angle

Linear fit residus from x=f(t)
Thermal expansion
Evaporation

For 5 nl/min :

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Dynamic flows

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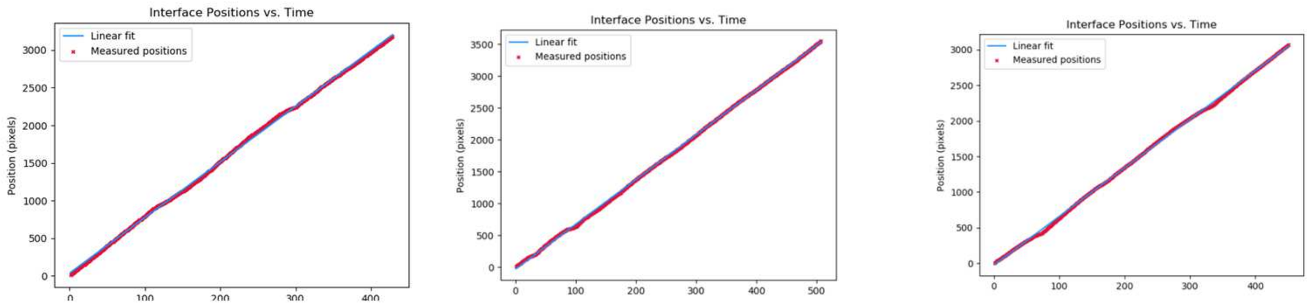
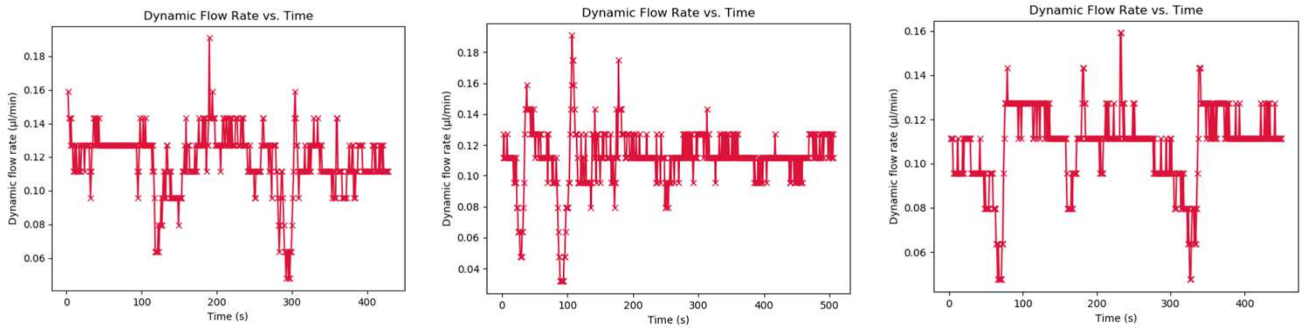
Generated flow rate = 100 nl/min

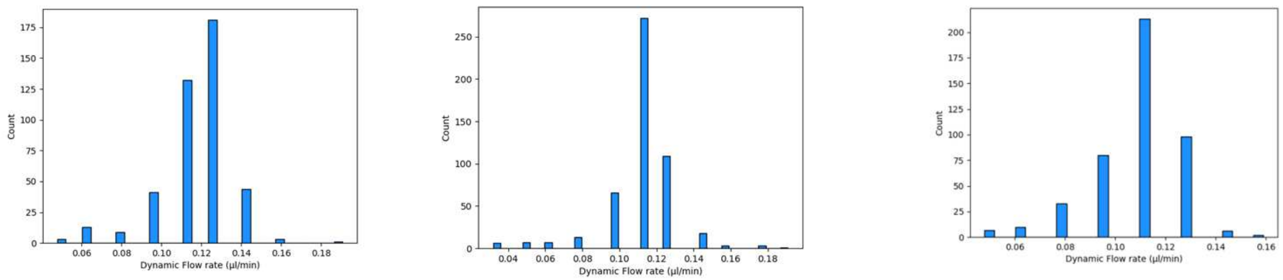
Determination of the mean flow rate



Dynamic flow rate
(1 point/s)



Dynamic flow rates distribution



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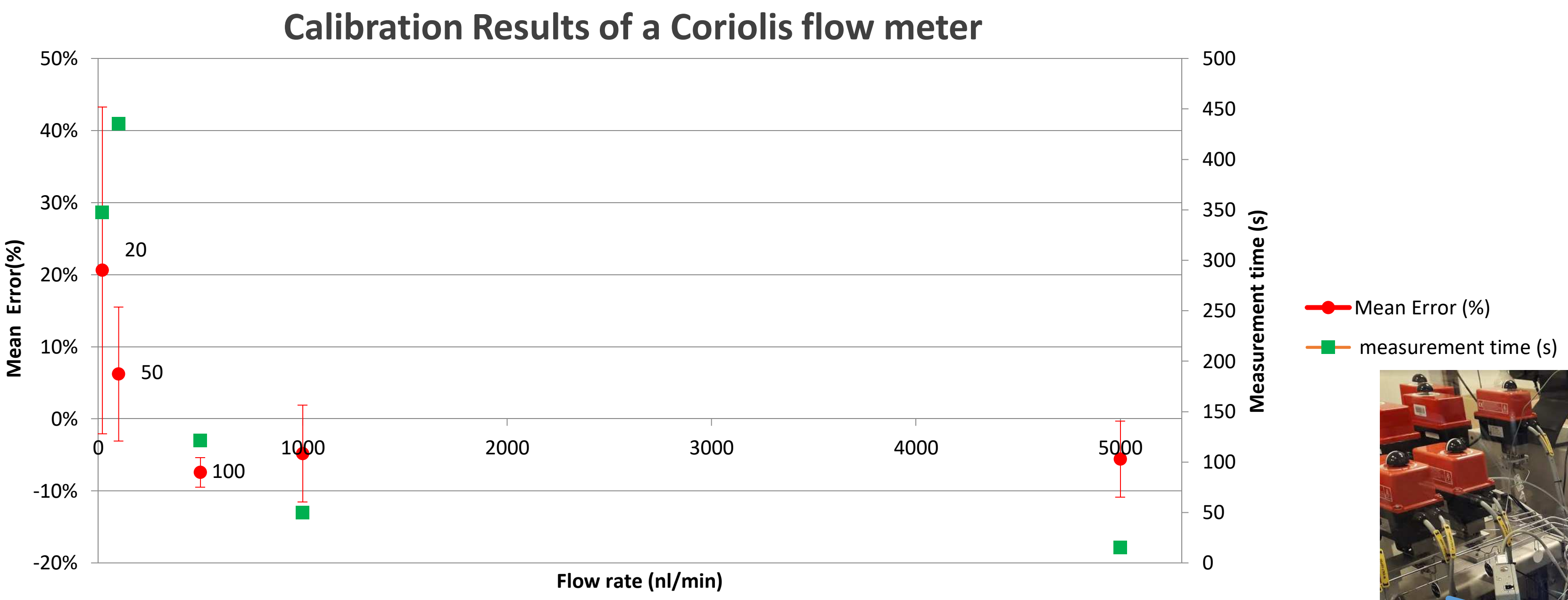
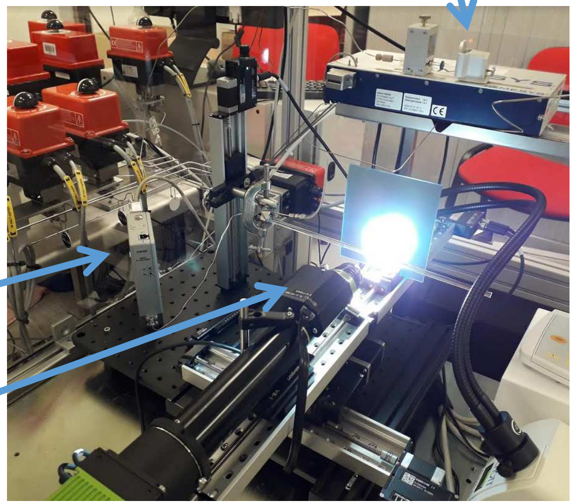
Interface Tracking: calibration example At CETIAT



Flow generator (syringe pump)



Flow meter under test

Front tracking system (reference flow rate)

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Interface Tracking setup at IPQ (Portugal)

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Interface Tracking at IPQ

CETIAT
ensemble, innover et valider

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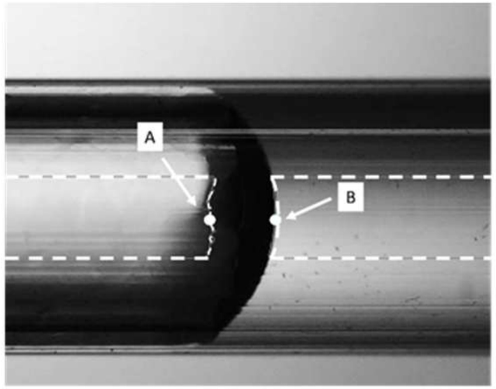
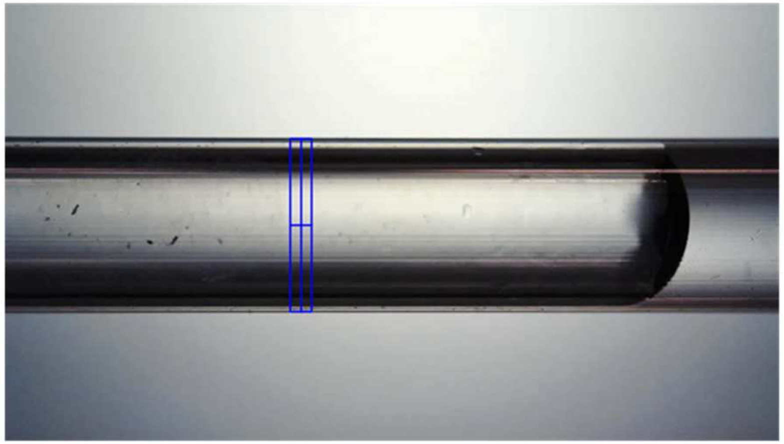
The experimental setup consists of using a high-resolution camera and an Phyton image processing software to track the distance traveled by the meniscus of a liquid in a capillary tube and calculate the flow rate.





To determine the position of the meniscus over time it was assumed as reference the position of the point that is in the axis of the capillary and coincident with the meniscus.

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Interface Tracking at IPQ

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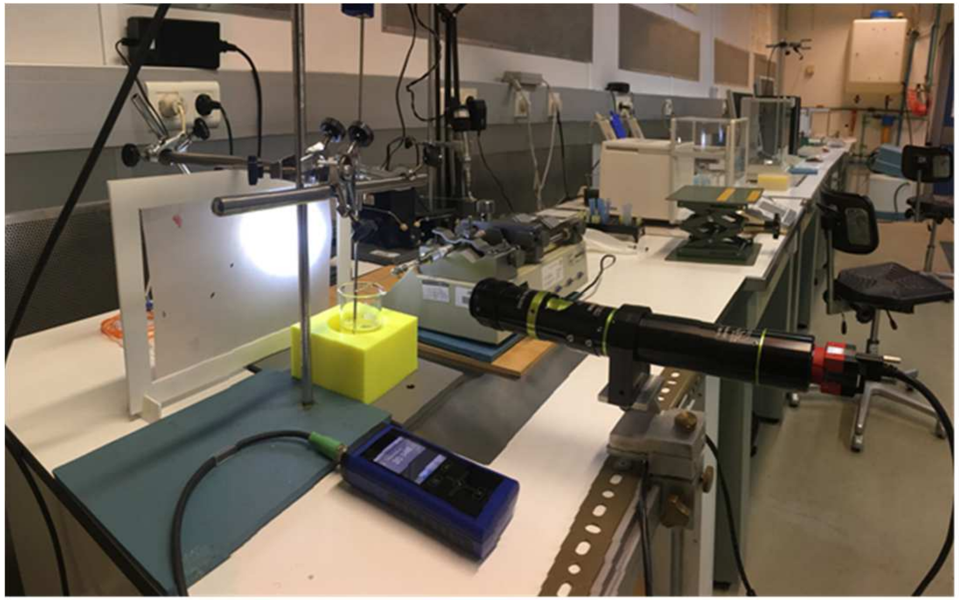

$$Q = \frac{x_2 - x_1}{\Delta t} \times \pi \times r^2 \times [1 - \gamma\,(T - 20)]$$

Can go down 1 µL/h with 7 % uncertainty

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Interface Tracking setup at THL (Germany)

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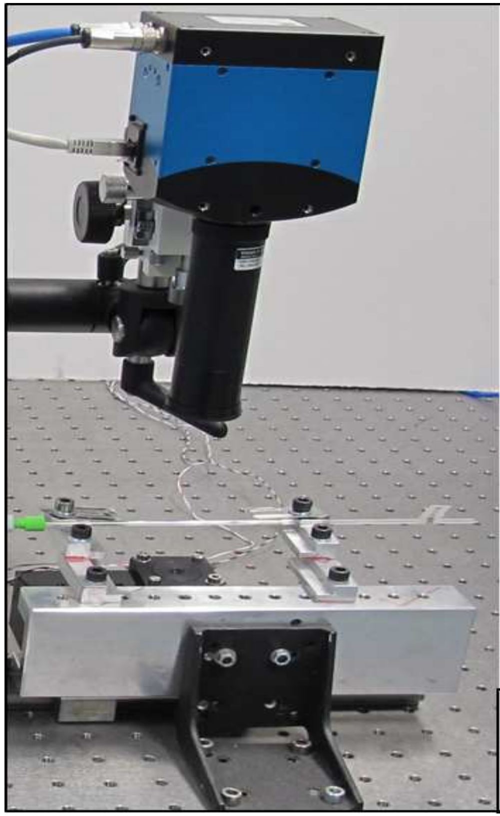
Interface Tracking at THL

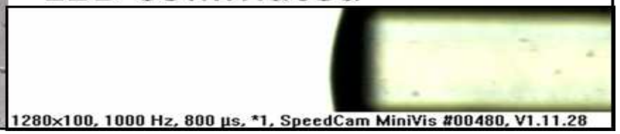


high speed camera

magnifying telecentric lense

capillary

Light source,
LED collimated



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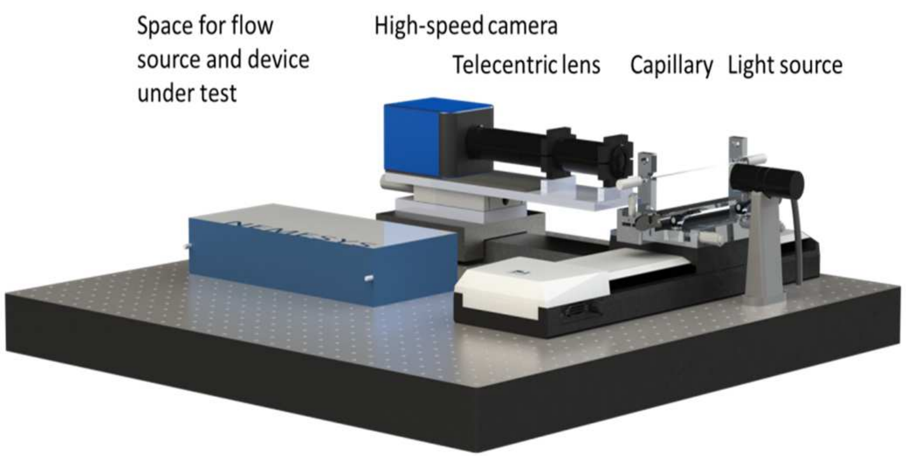
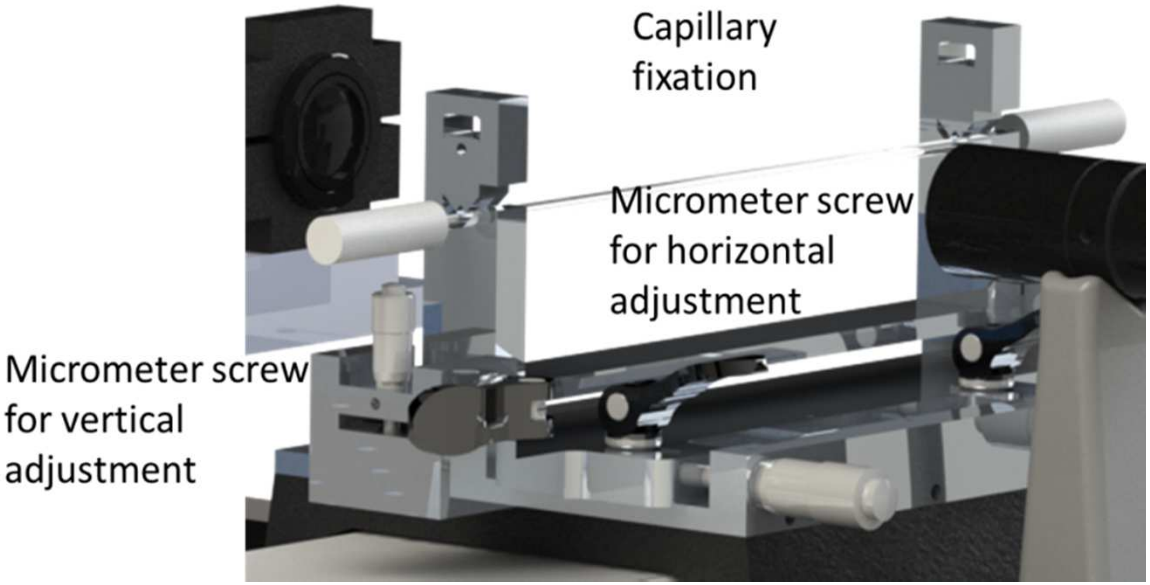
Interface Tracking at THL





facility used between 50 nl/min and 500 µl/min.

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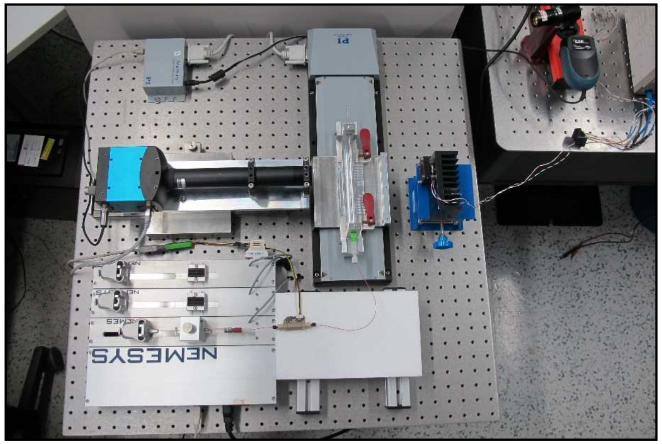
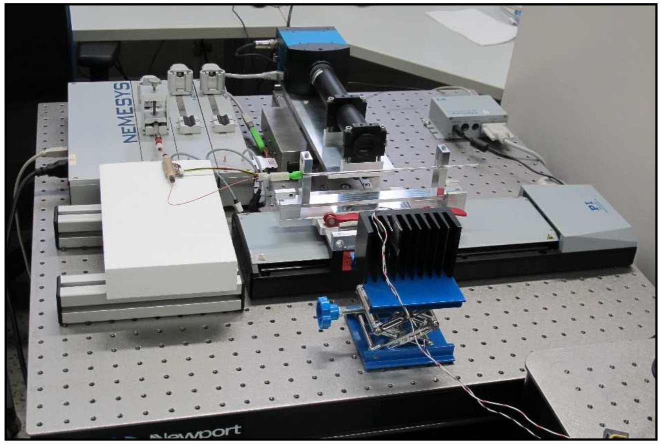
Interface Tracking at THL

Components

1. Optical table
2. High speed camera
3. Light source
4. Precision Linear Stage
5. Device under examination
   - Flow dosing unit
   - Flow sensor
   - Capillaries





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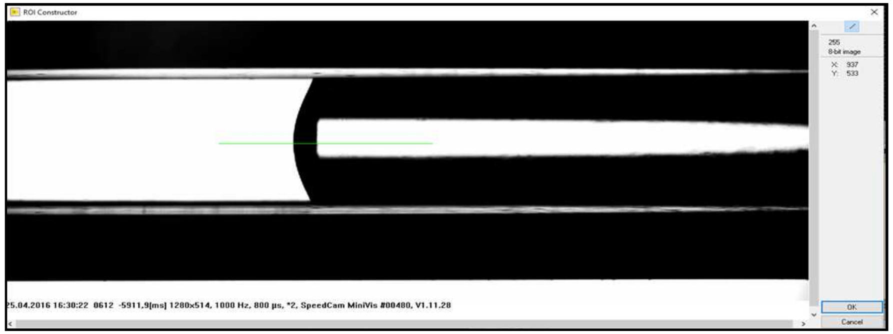
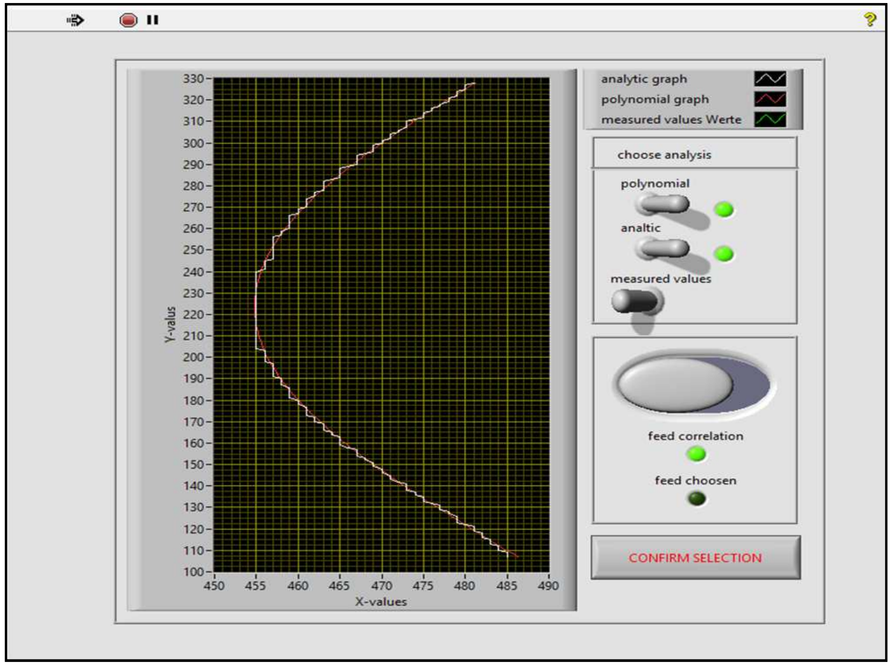
Interface Tracking at THL





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Pendant Drop Method at CETIAT (France)

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Pendant Drop method at CETIAT

CETIAT ensemble, innover et valider

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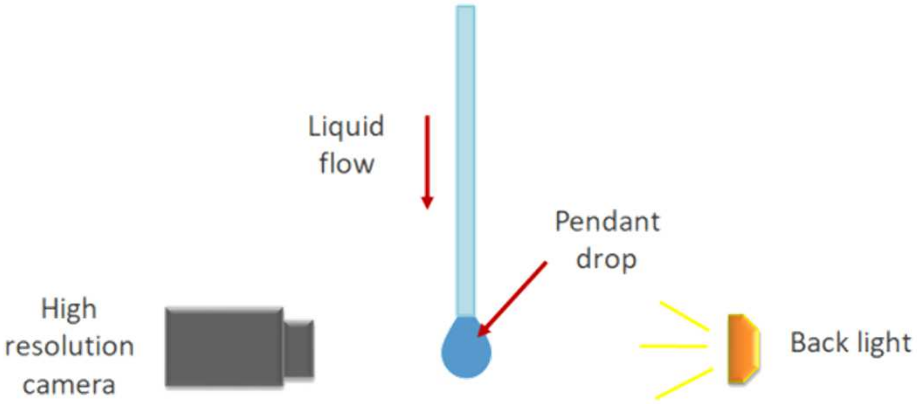
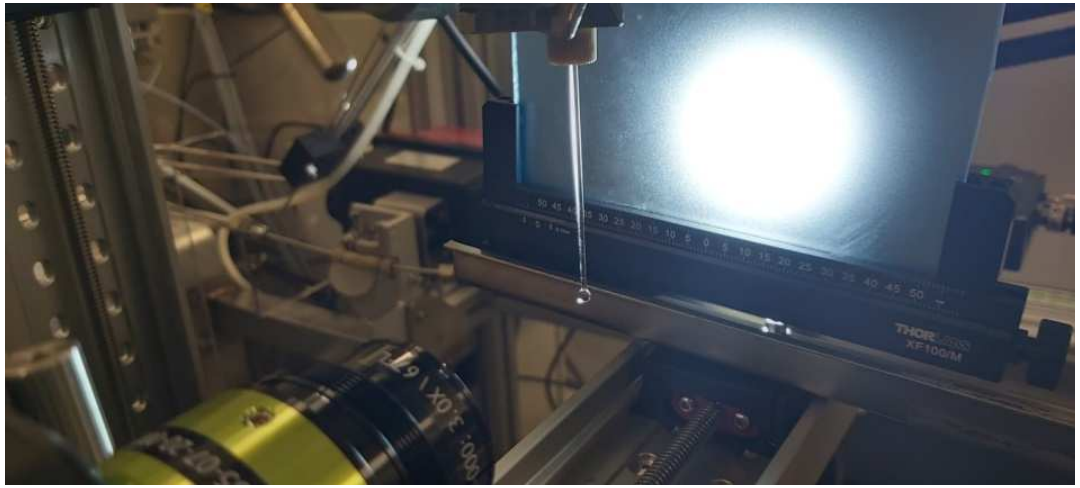
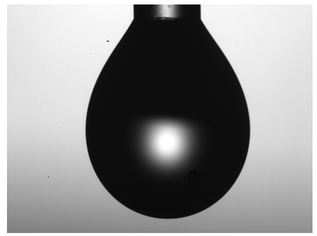




Measurement of the change in the droplet's volume over time under a liquid flow

$$Q_V = \frac{\Delta V_{droplet}}{\Delta t}$$



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Pendant Drop method at CETIAT

CETIAT ensemble, innover et valider

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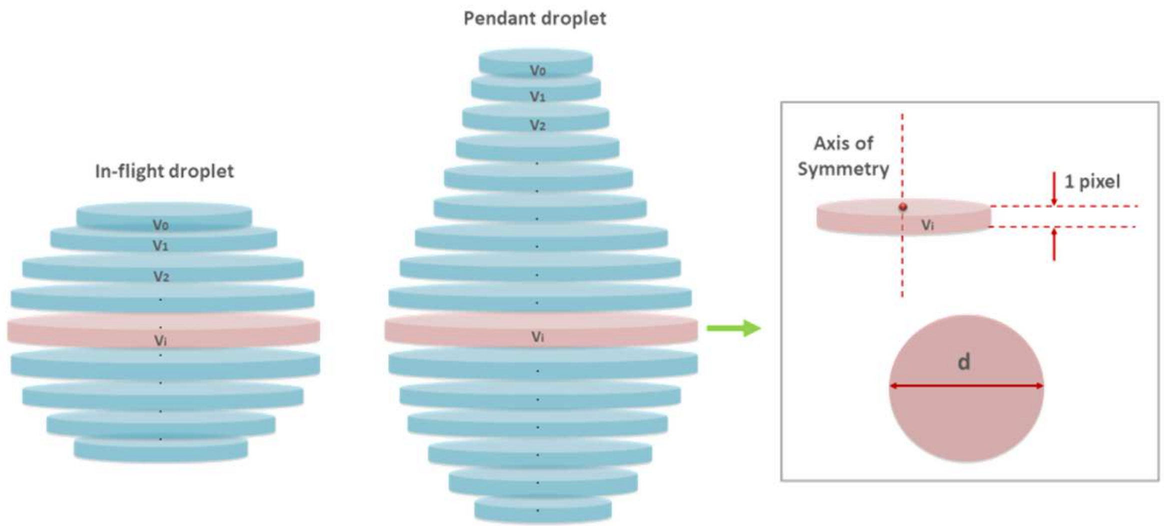

$$V_{droplet} = \sum_{i=1} V_i = \sum_{i=1} \frac{\pi}{4} d_i^2 . h$$

$$Q_V = \frac{\Delta V_{droplet}}{\Delta t}$$

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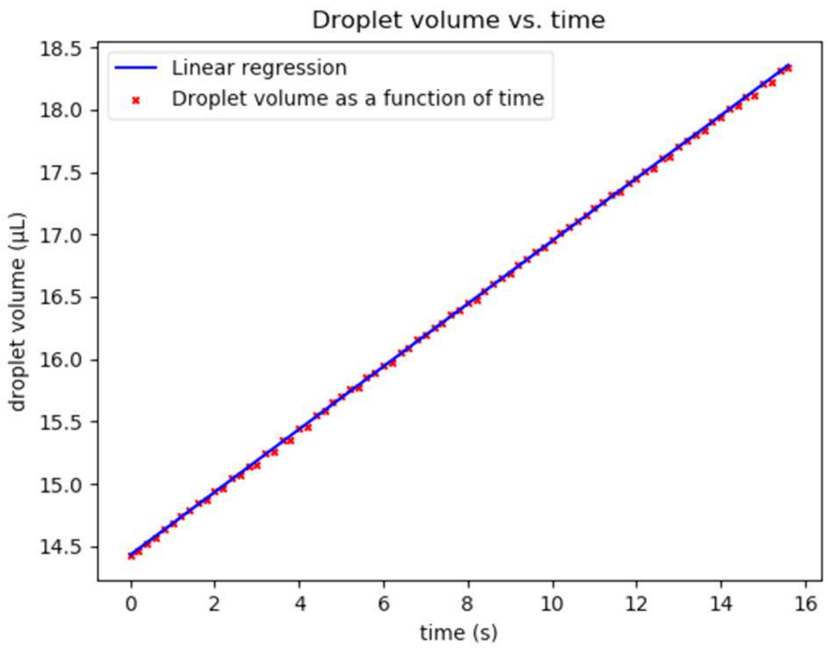
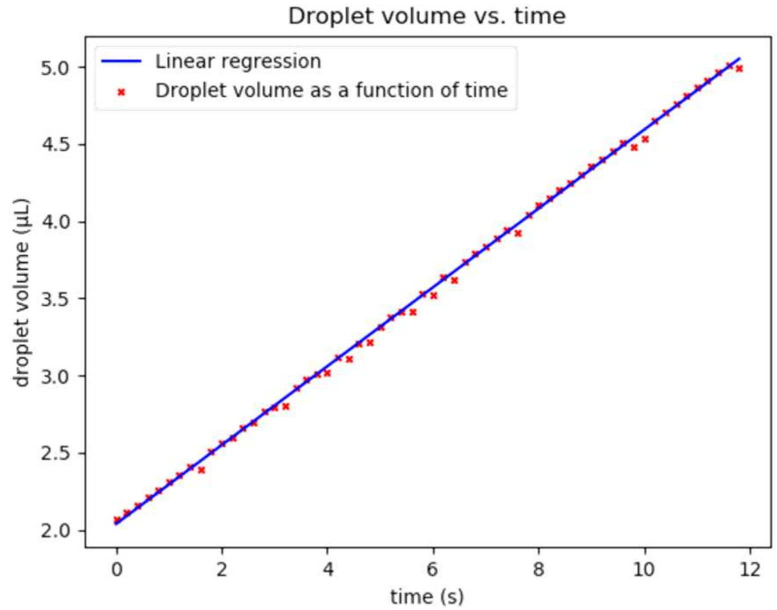
Pendant Drop method at CETIAT



Q = 15,10 µl/min



Q= 15,31 µl/min

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Pendant Drop Method at IPQ (Portugal)

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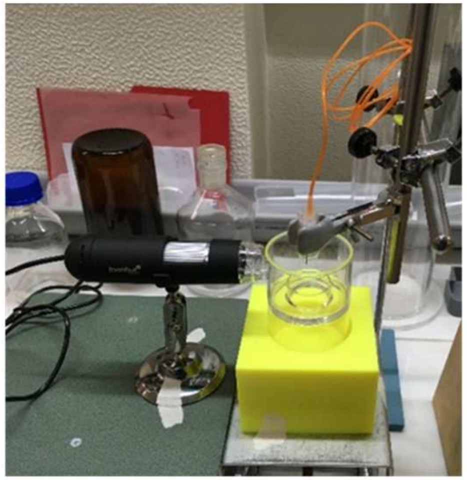
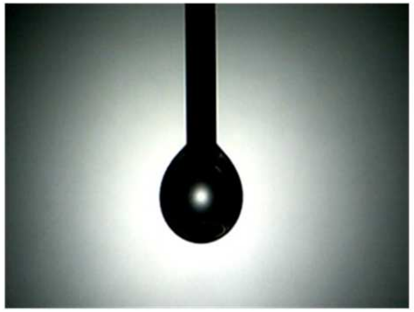
Pendant Drop method at IPQ

The delivered liquid flow was determined by observing the volume increase of a drop at the end of the flow line placed inside an evaporation trap.





This observation was performed at a specific time by using photographs taken by a digital USB microscope with 400X magnification and a Phyton software for image treatment.

$$Q = \frac{\Delta V}{\Delta t}$$

EMPIR EURAMET

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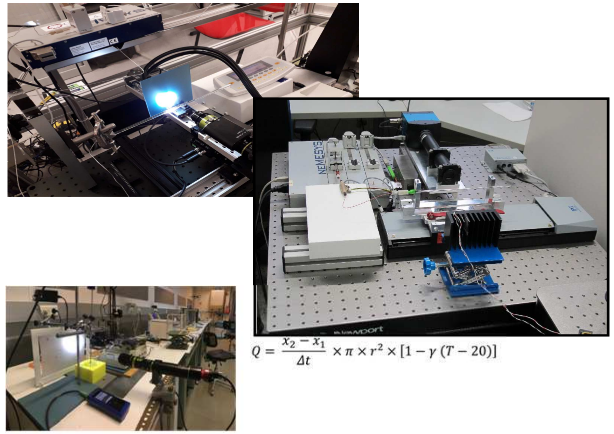
CONCLUSION

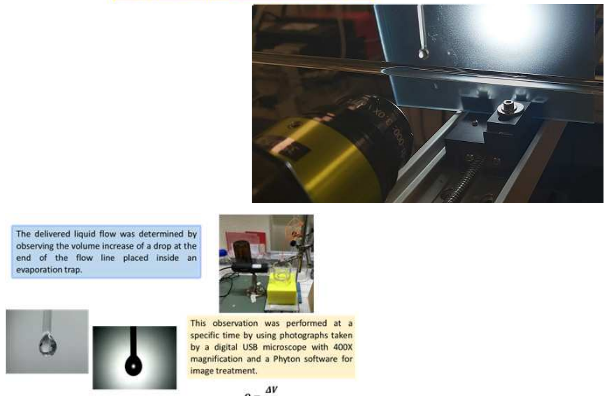
1. Interface tracking method
   - ➢ Principle (example at CETIAT)
   - ➢ Uncertainty budget (example at CETIAT)
   - ➢ IPQ & THL Interface Tracking Setups



$$Q = \frac{x_2 - x_1}{\Delta t} \times \pi \times r^2 \times [1 - \gamma\,(T - 20)]$$

Can go down 1 µL/h with 7 % uncertainty

2. Pendant drop method
   - ➢ Principle (example at CETIAT)
   - ➢ IPQ Pendant Drop setup



$$Q = \frac{\Delta V}{\Delta t}$$

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