Development of an optical measurement method for “sampled” micro-volumes and nano-flow rates

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Outlook

- Background
- Needs
- Description of the system
- Description of sampling and measurement process
- Experimental results, uncertainty components
- Future developments

Background

- Nuclear Medicine → Scintigraphy → P.E.T.
  - **Use of short-lived β^+ radionuclides:**
    - ^{18}F ($T_{1/2}$ = 109,728(18) min)
    - ^{15}O ($T_{1/2}$ = 2,041(6) min)
  - **Currently the measurement of activity is done on site with ionization chambers … which must be calibrated (U = 5 to 15 %)**
  - **For shortest periods there is currently no traceability to national standards**
  - **Need for development of a primary measuring device for *in situ* measurements**

Needs

- Measurement uncertainty depends on:
  - Uncertainty on the measured **volume** (quantity of solution)
  - Uncertainty on the measurement **duration** (activity decreasing between sampling and measurement)
  - Uncertainty on the **detection efficiency** (relation between counting rate and activity)

- Measured volume and sampling duration have to be traceable to national standards.
- **Target uncertainty (k=2) < 2 %**

- In order to measure **high activity liquids** :
  - Measured **volume** needs to be **as low as possible (below 1 µL)**
  - Global **detection efficiency** has to be **low**
  - Detection system has to **handle high counting rate**

- The system must **withstand irradiation** and wetted elements must be **replaceable**
- Some of these needs are **contradictory** (eg low yield but low uncertainty), it will requires a system optimization

Research Projet

- To develop a **radiopharmaceutical primary calibrator prototype**
  - **LNHB** (French DI for ionizing radiations) to develop **the activity measurement system**
  - **LNE-CETIAT** (French DI for liquid flow and micro-flow) to develop **the sampling and volume measurement system**

- **National funding** (LNE-DRST), 3 years project (**2017-2020**)

- **Traceability** to **activity**, **length** and **time** standards

- Validated by comparison to existing primary standards (gravimetry & IR standards)

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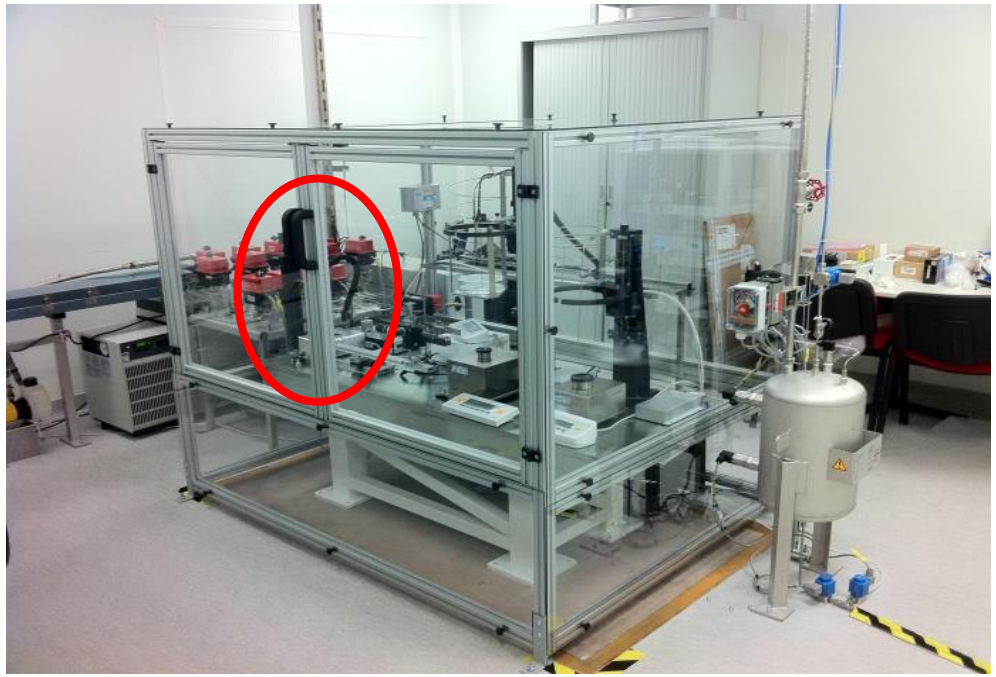
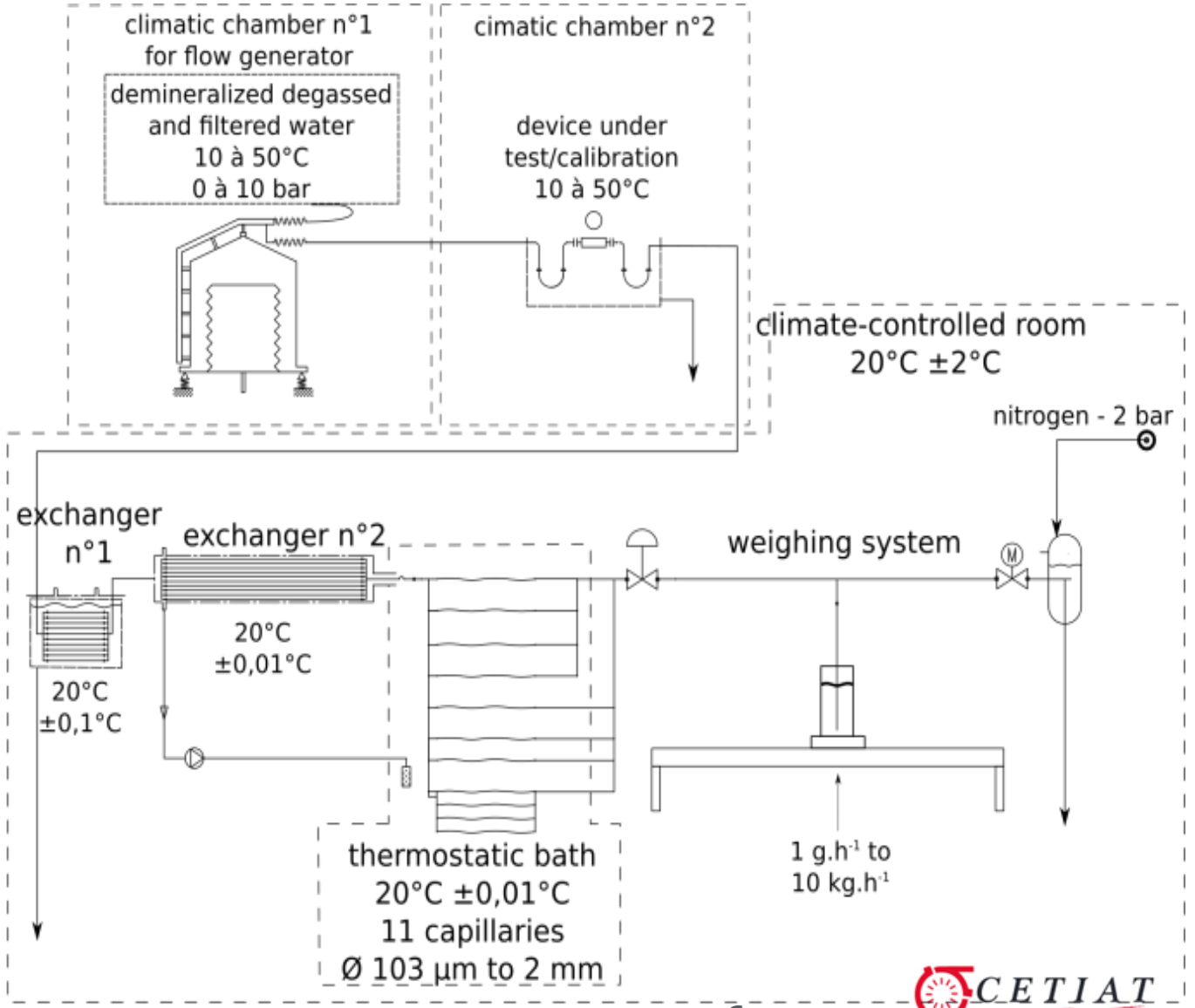
CETIAT's liquid micro-flow standard

- Gravimetric method
- 1 $g.h^{-1}$ to 10 $kg.h^{-1}$
- 0.2 barg to 10 barg
- 10 °C to 50 °C





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Microvolume sampling and measurement system

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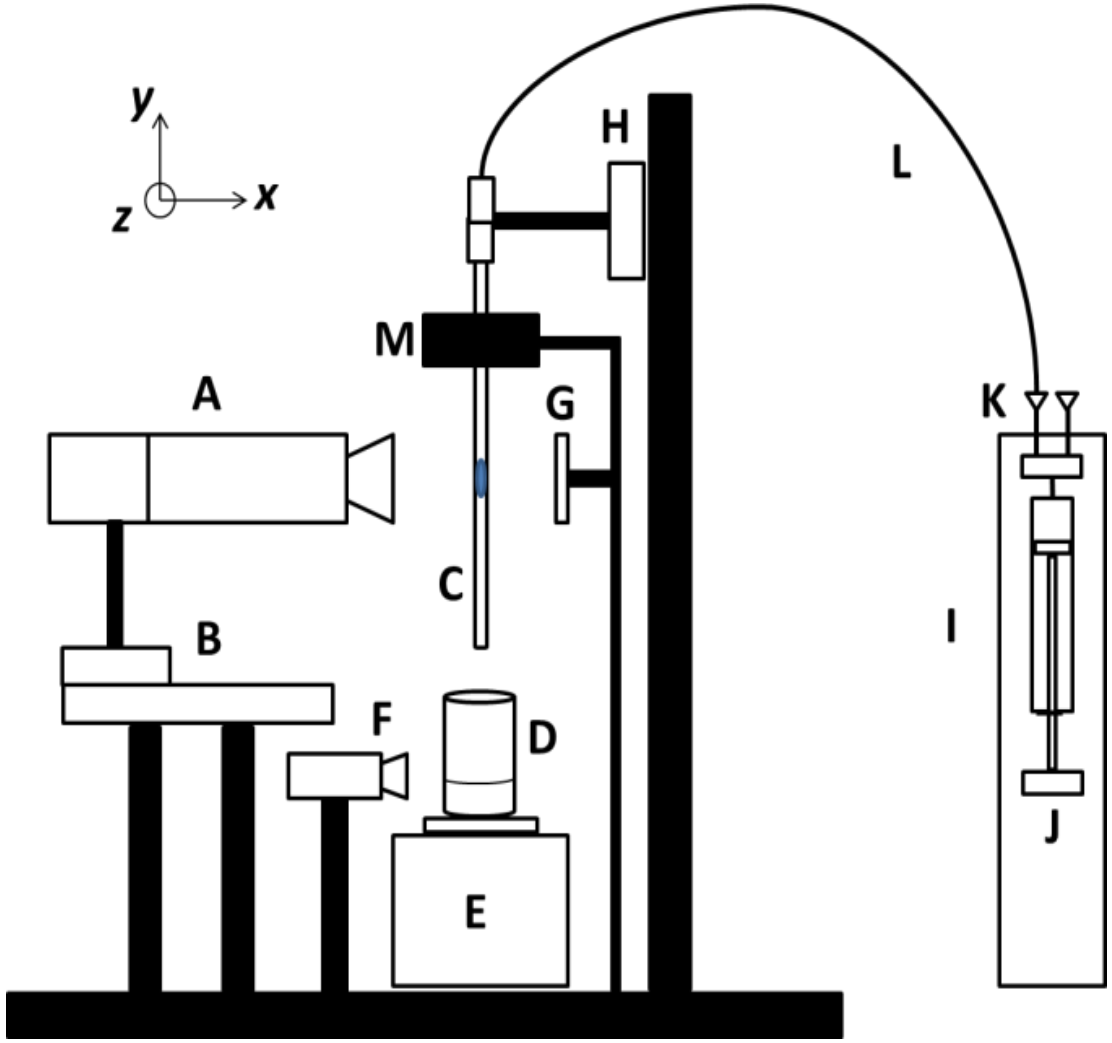

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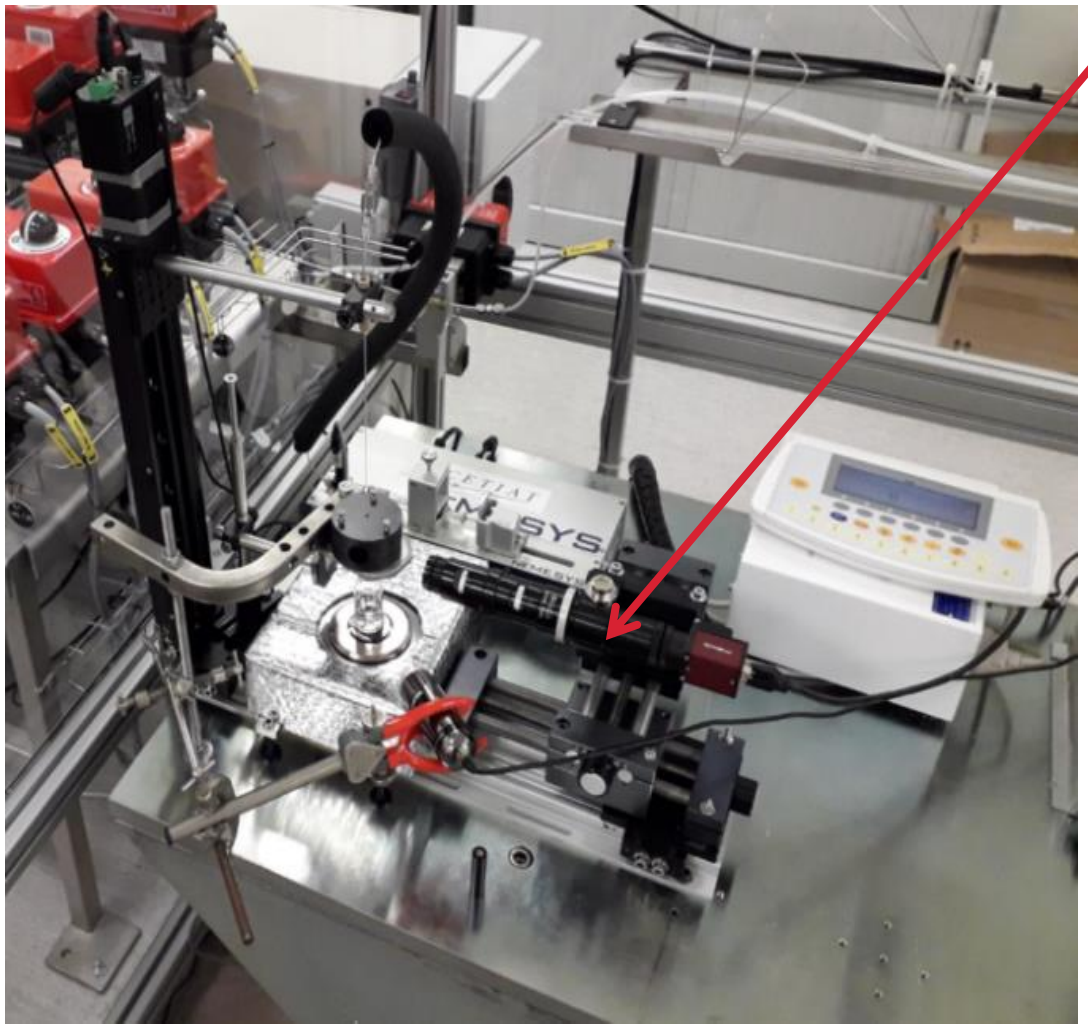

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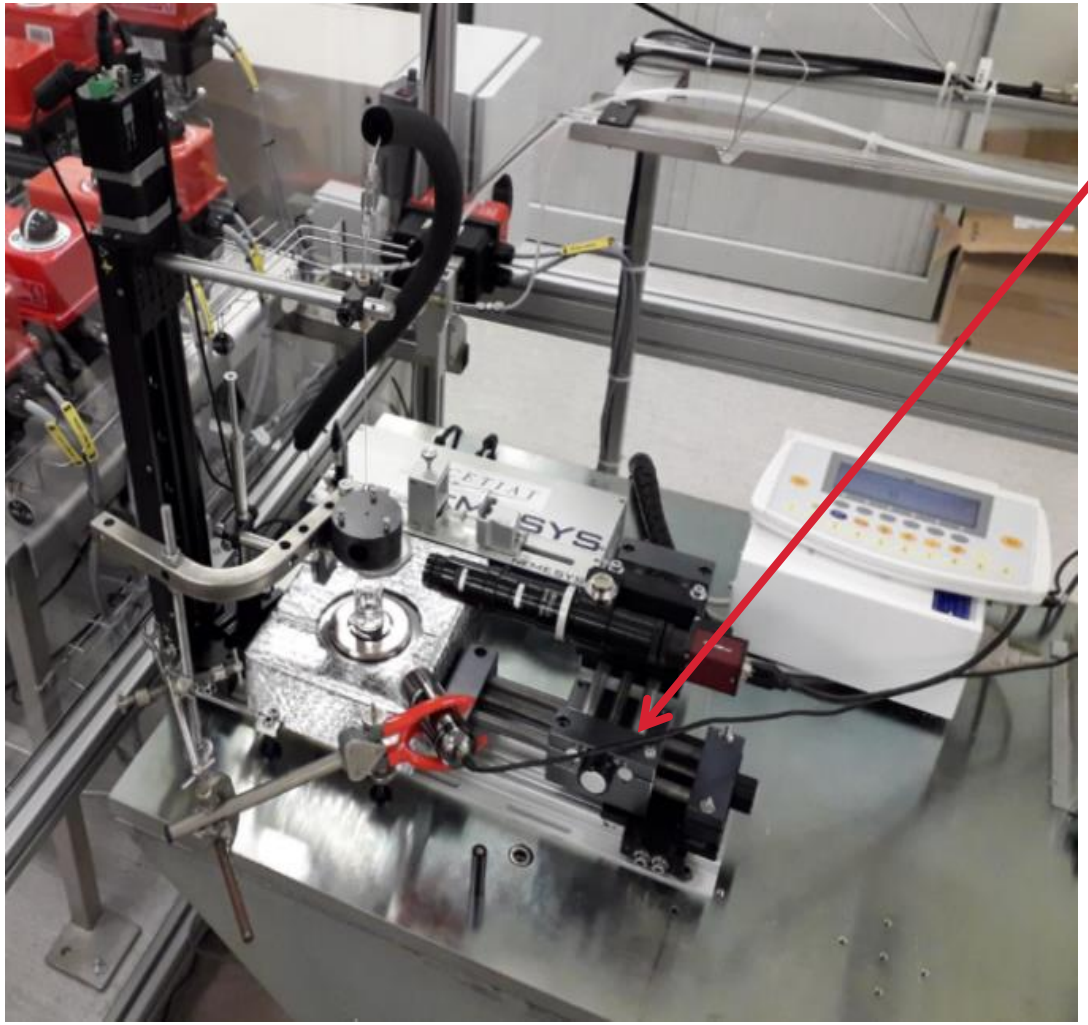

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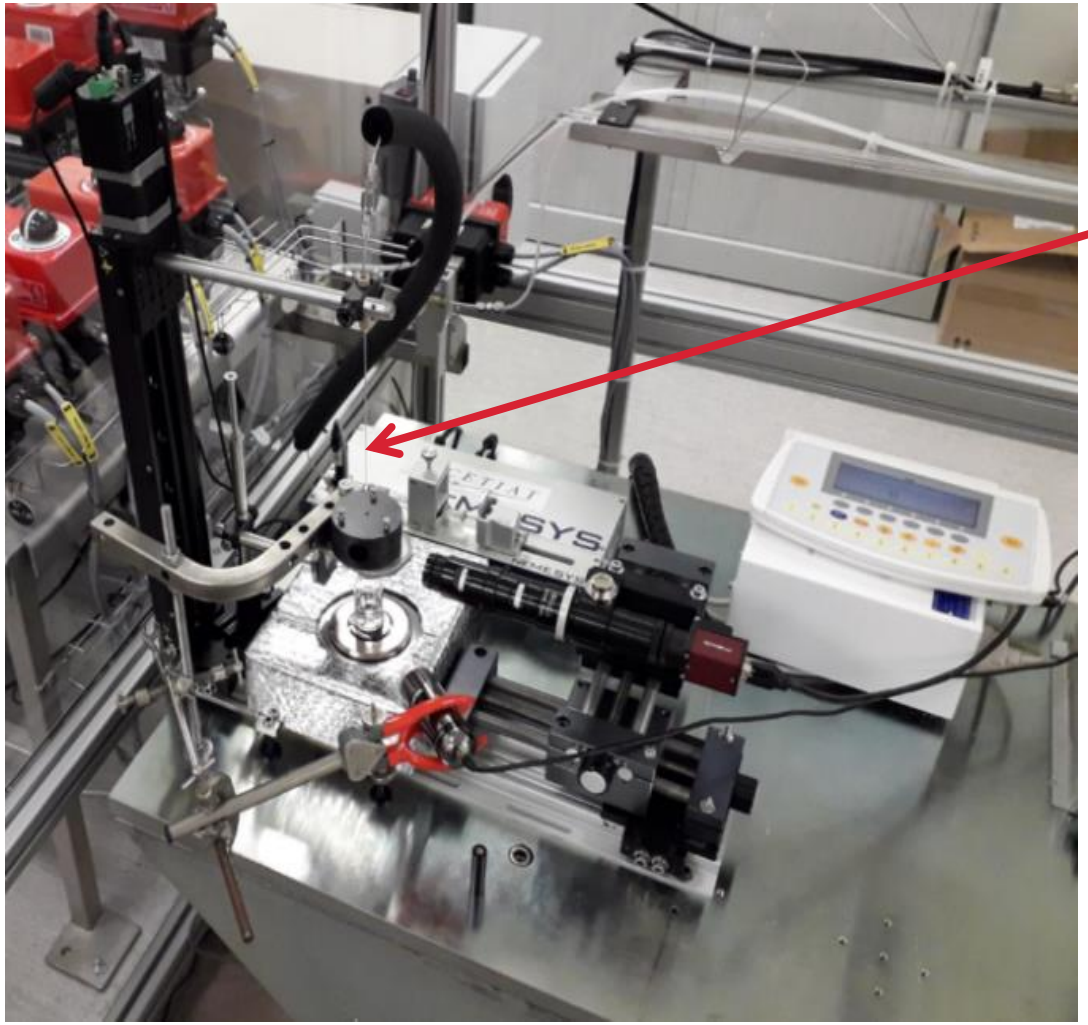

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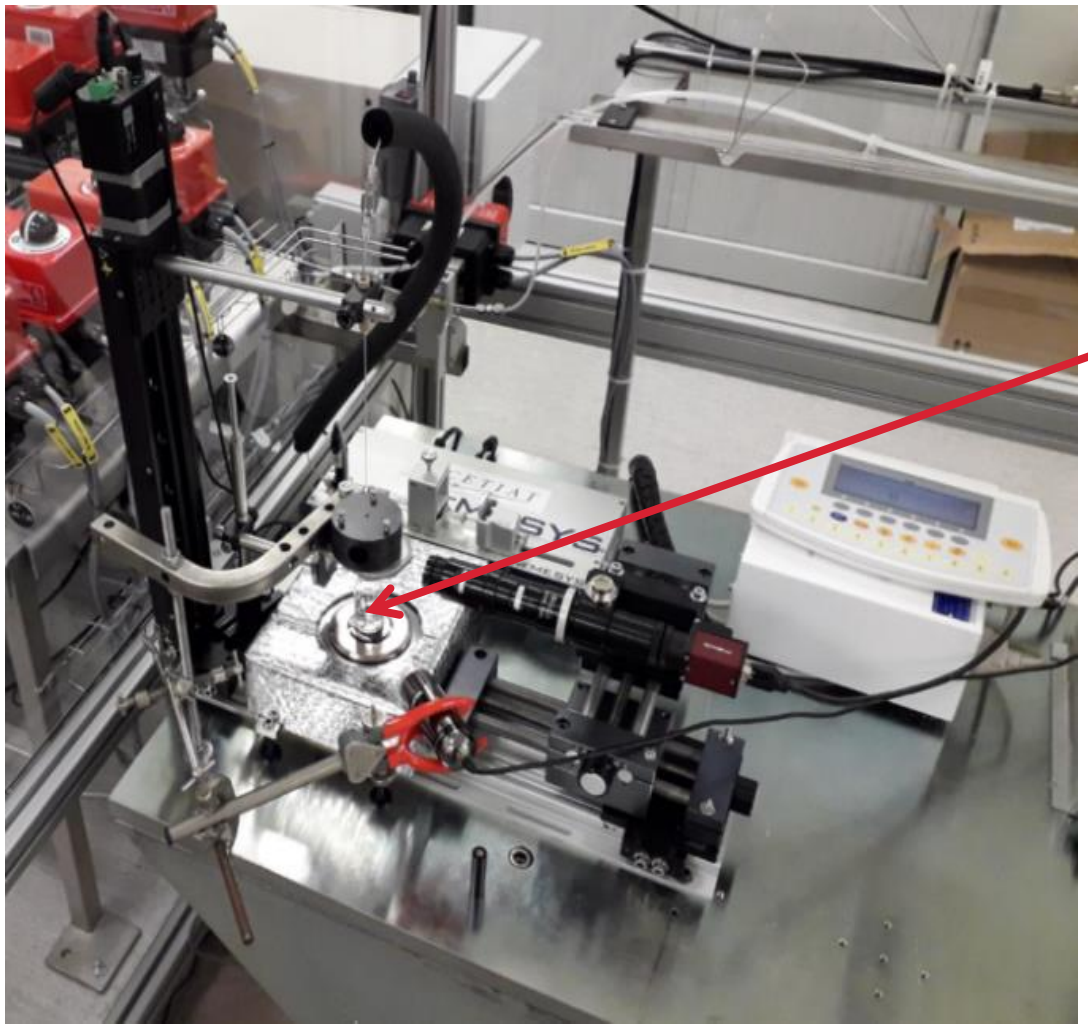

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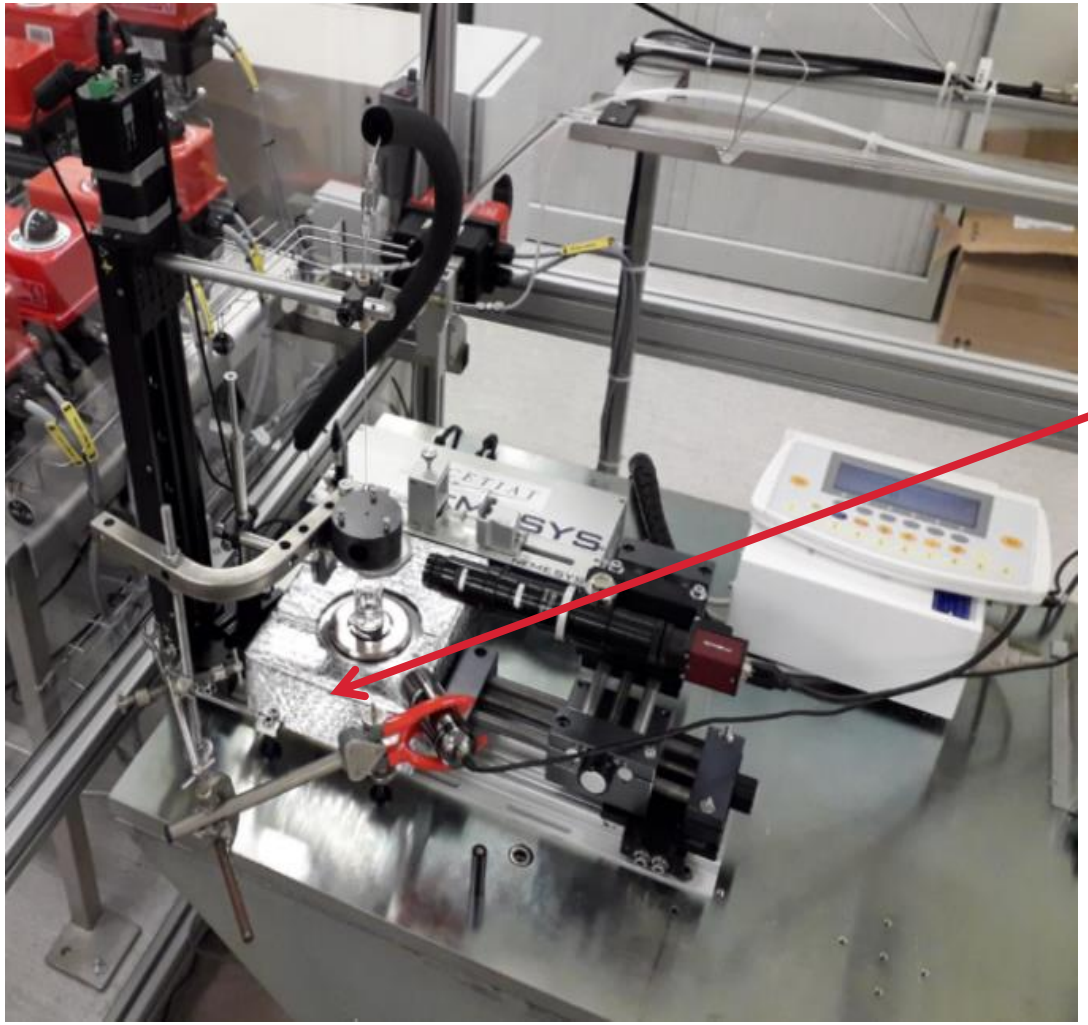

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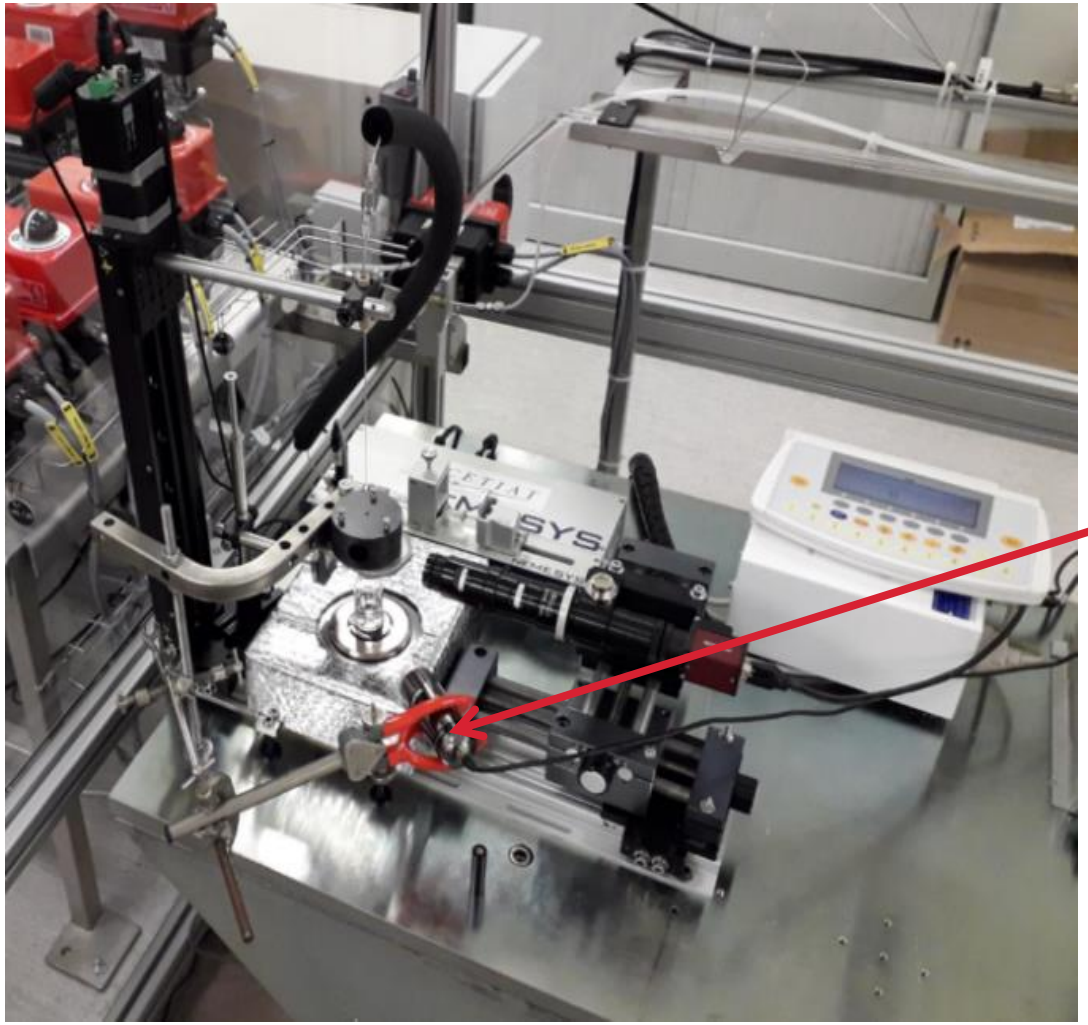

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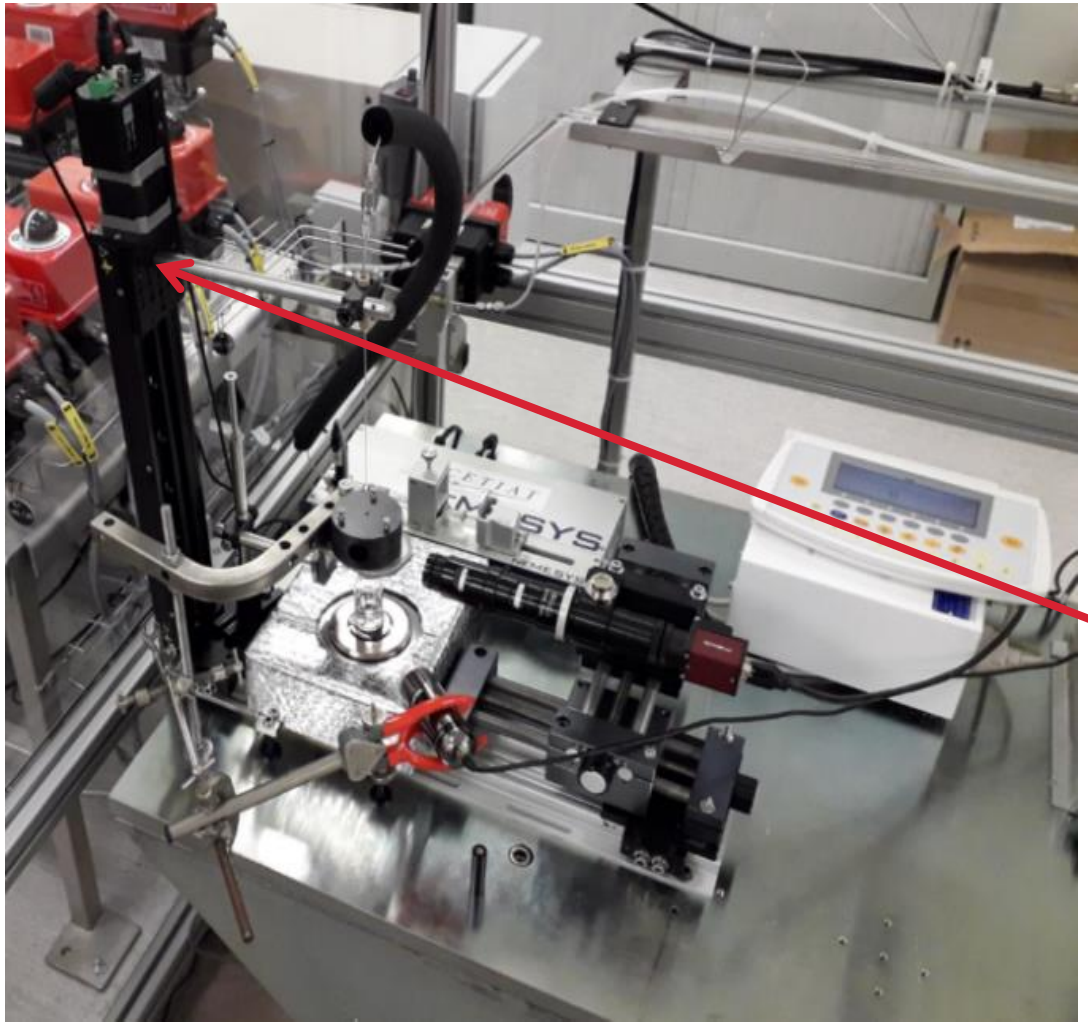

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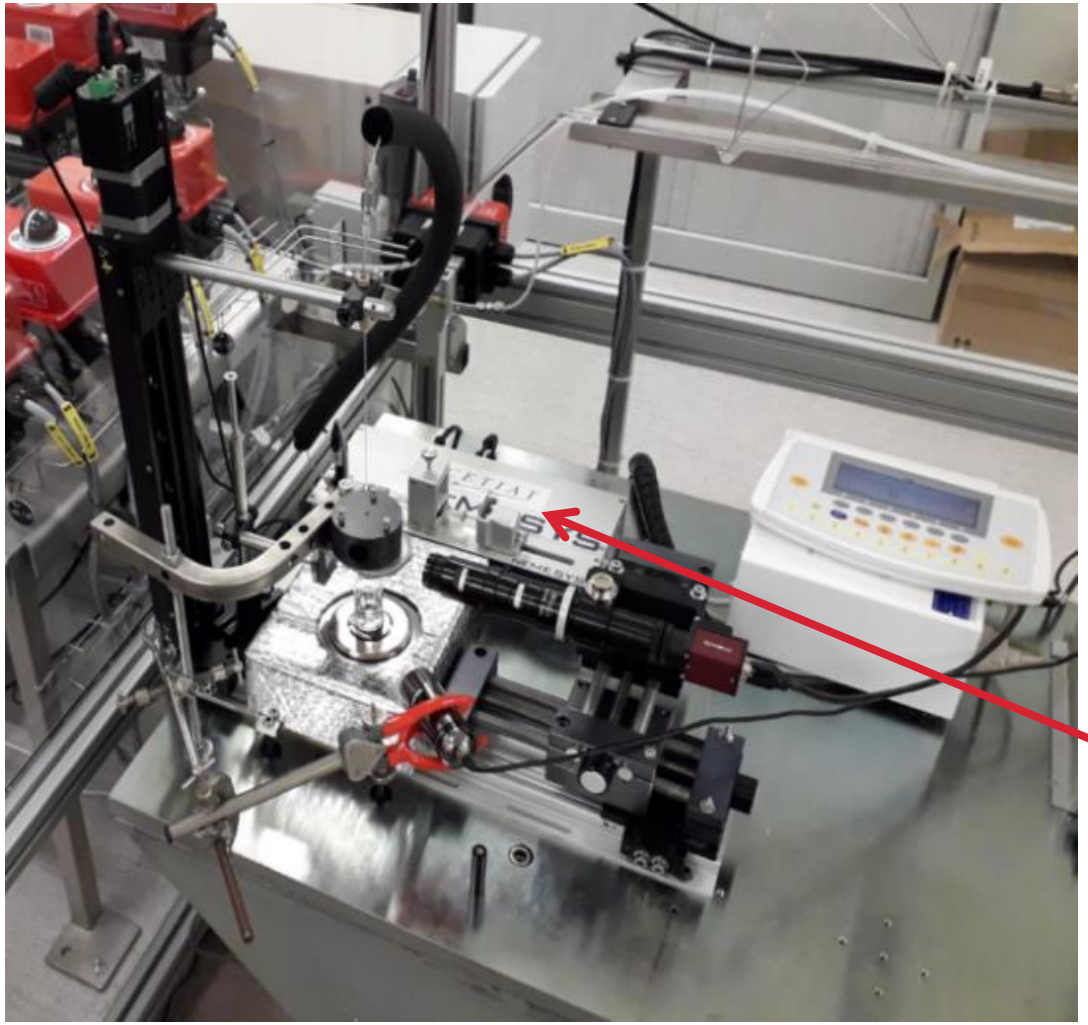

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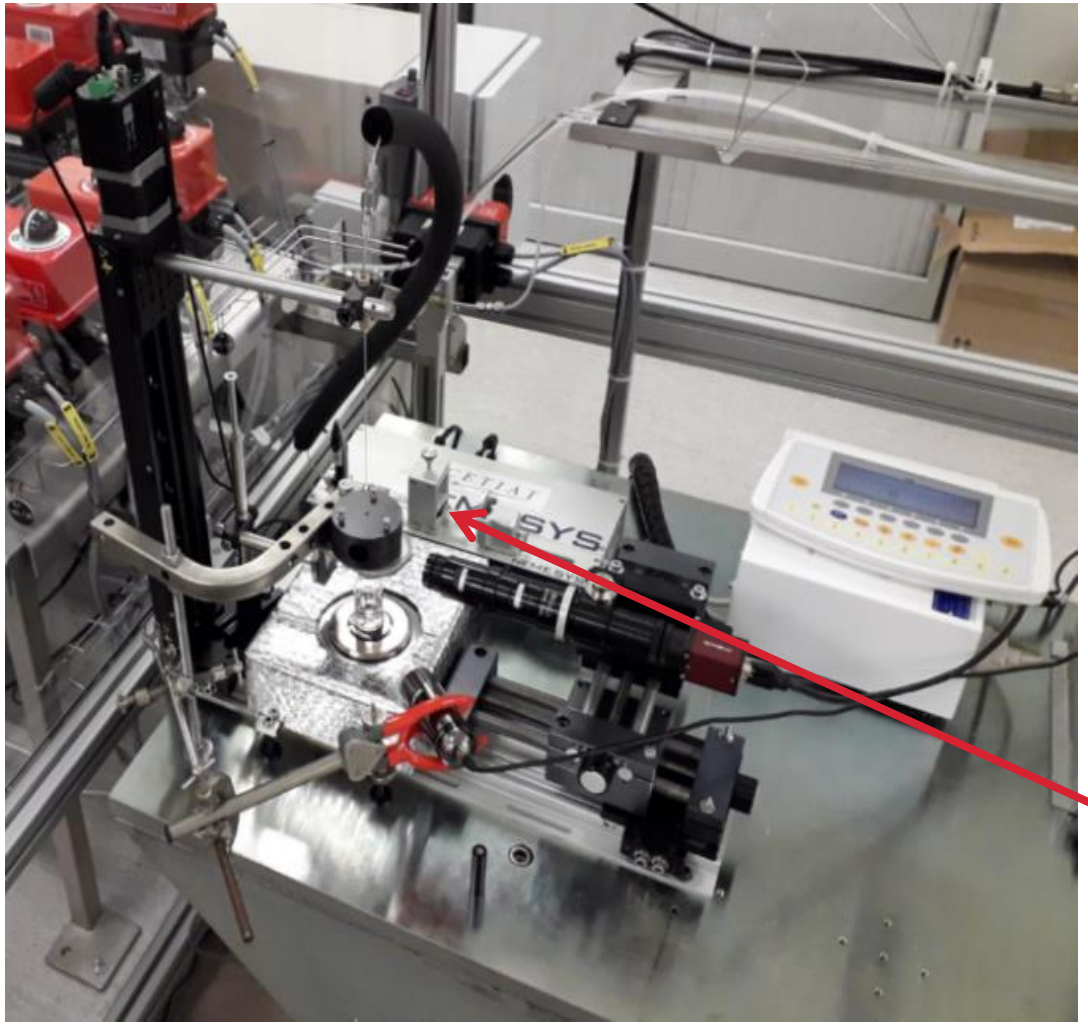

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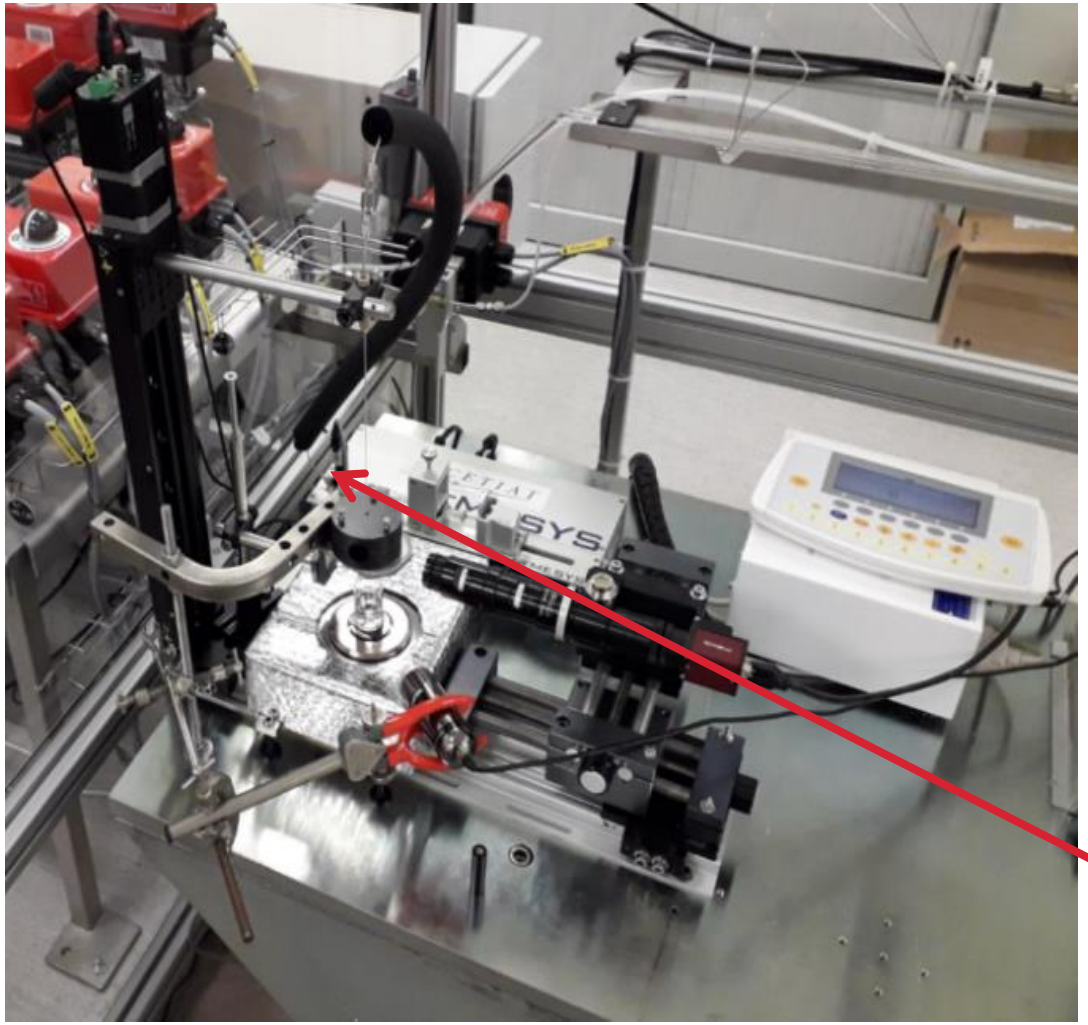

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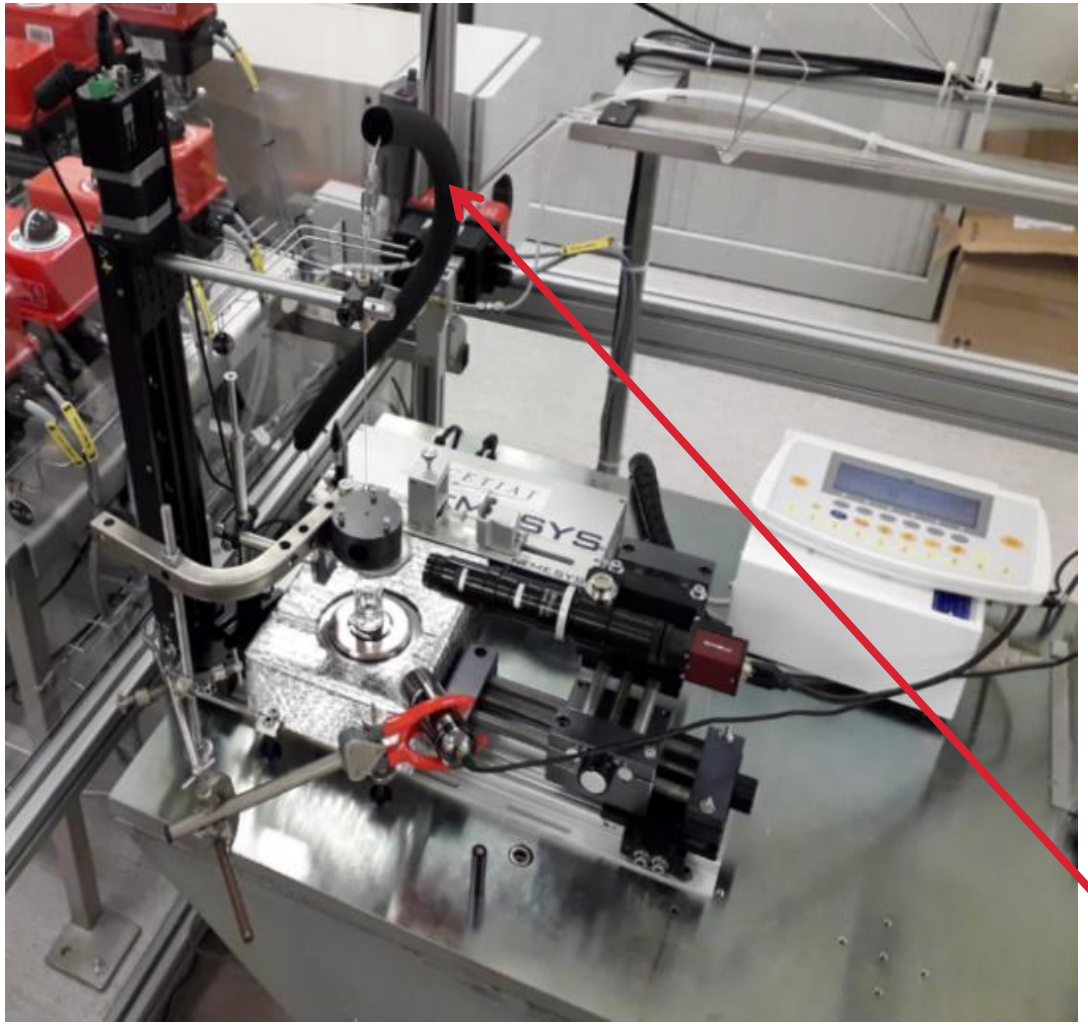

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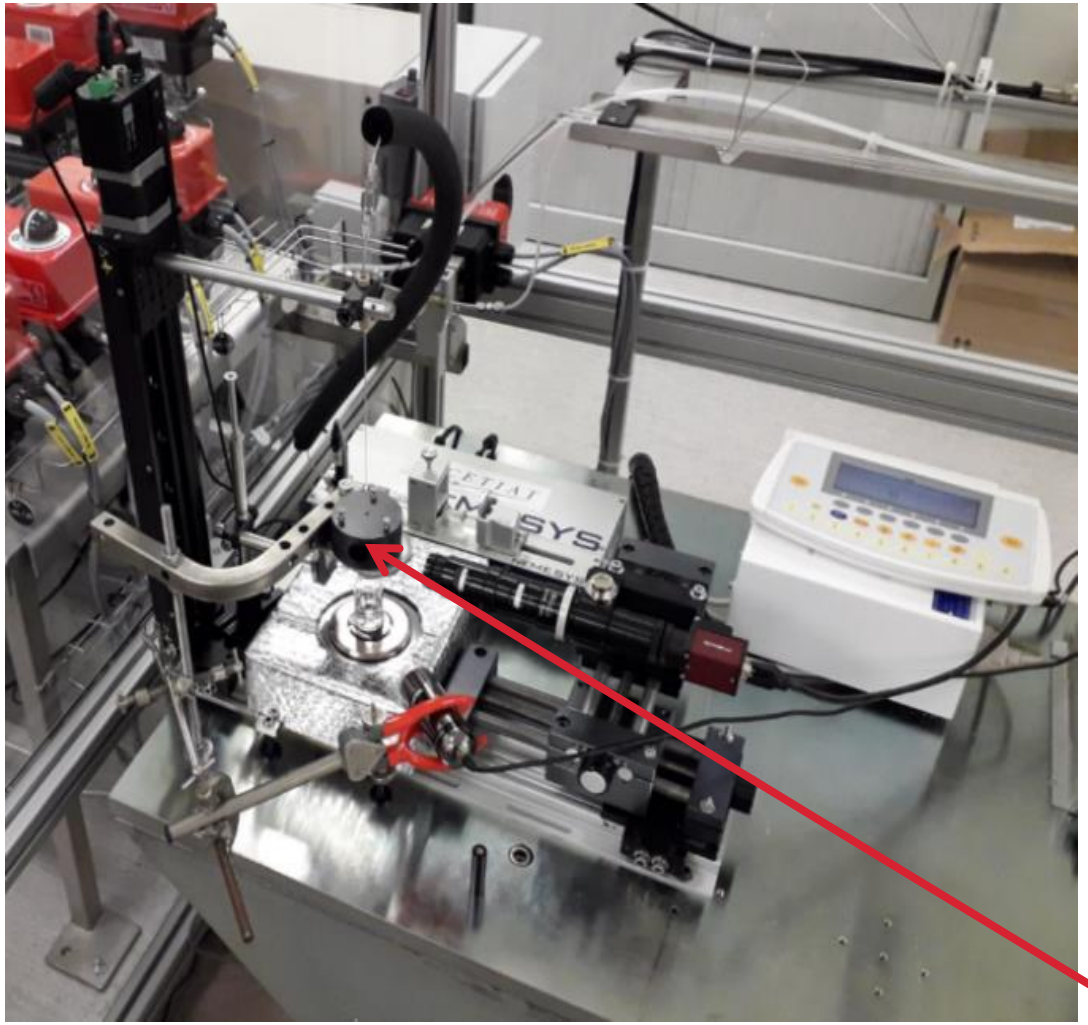

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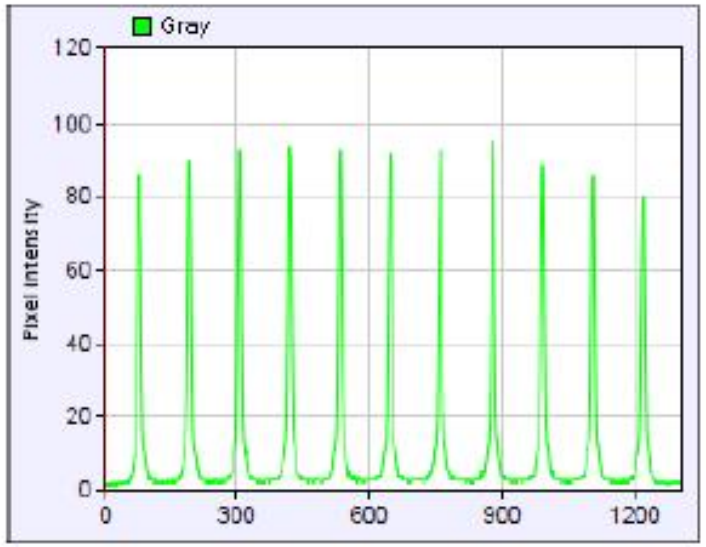
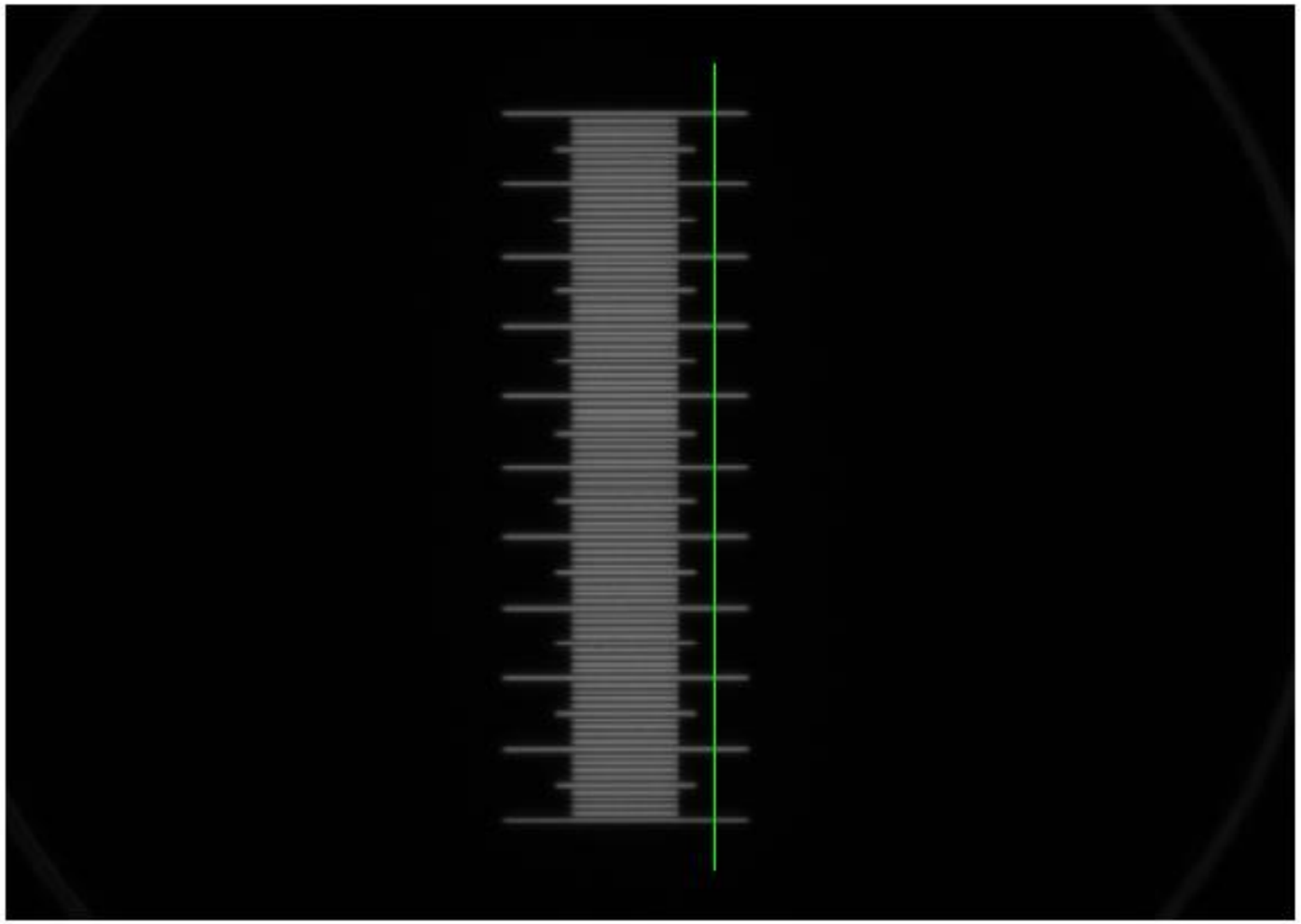
STEP 1

Traceability: calibration of the camera (pixel size)





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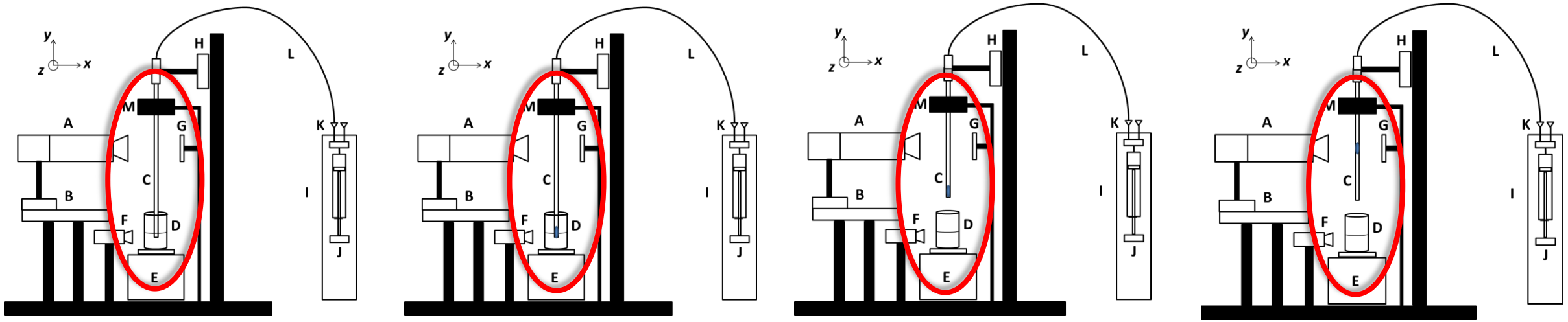
STEP 2
Microvolume sampling (+gravimetric comparison)

Immersion of capillary | Sampling | Rising of capillary



1
Immersion of capillary

2
Sampling

3
Rising the capillary

4
Moving microvolume In imaging field

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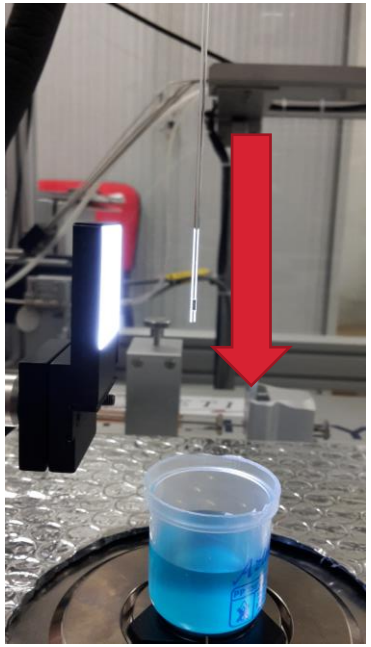
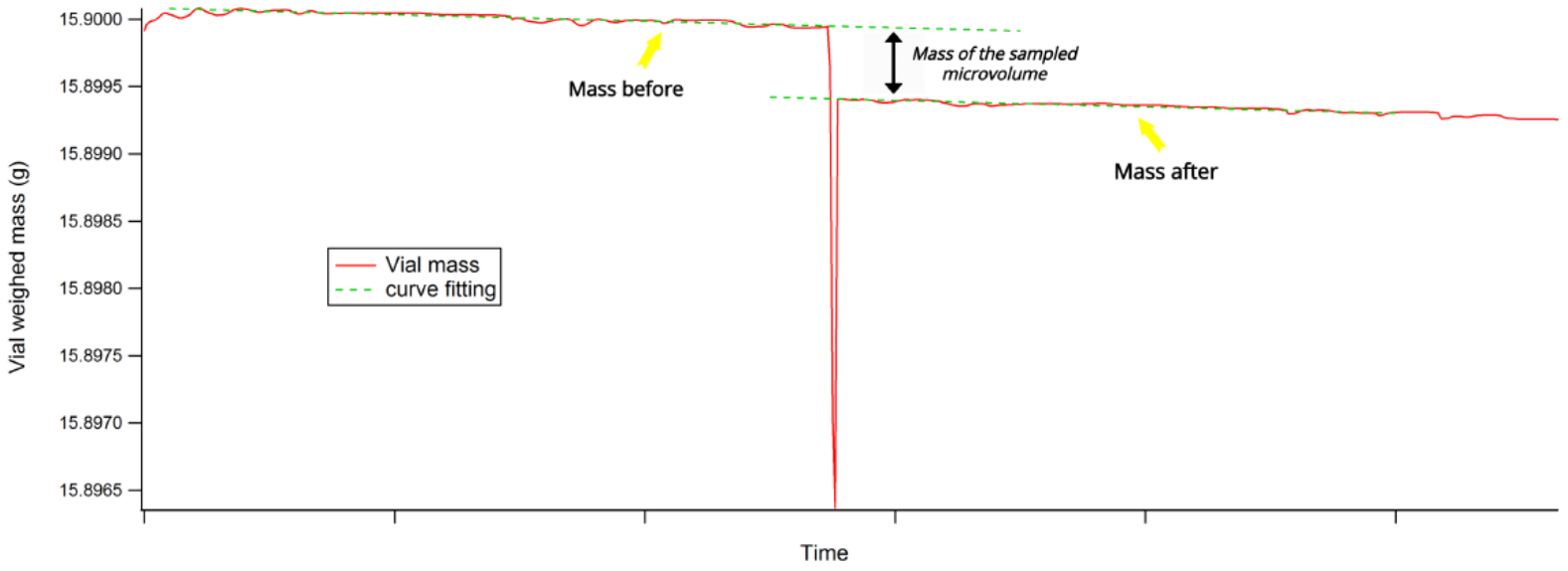
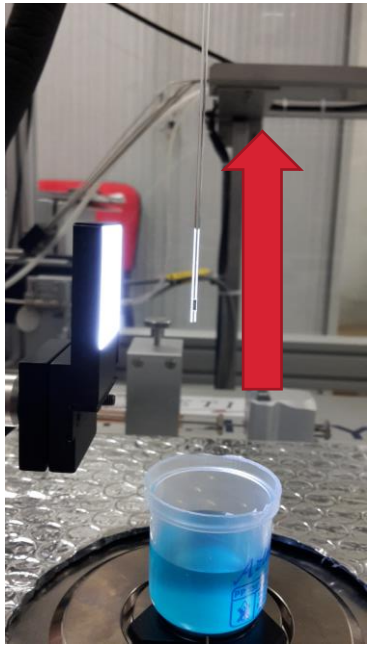
STEP 2
Microvolume sampling (+gravimetric comparison)

Immersion of capillary → Sampling → Rising of capillary







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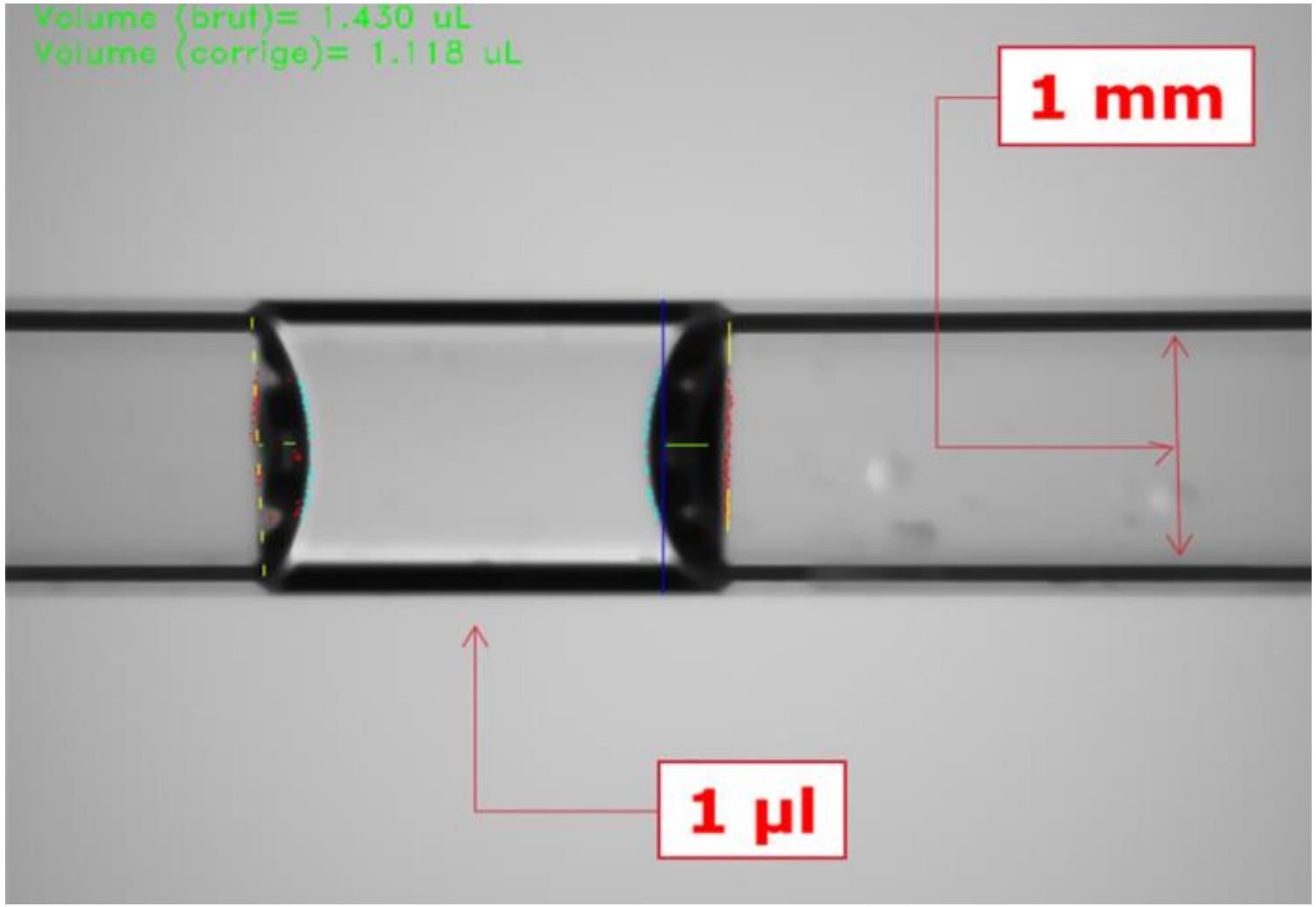
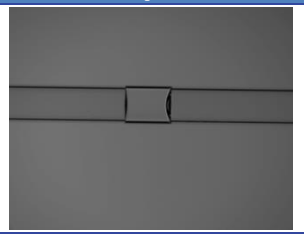
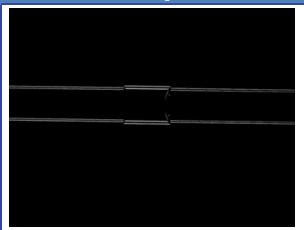
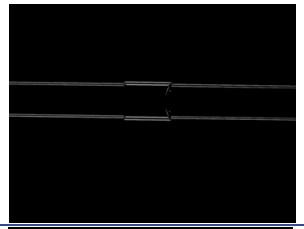
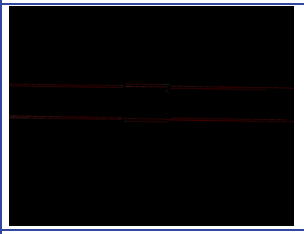
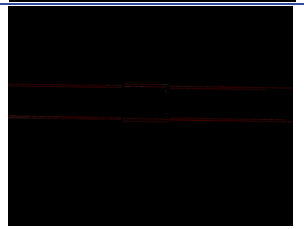
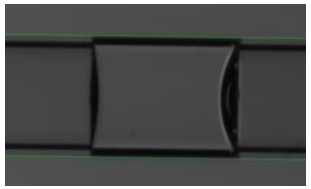
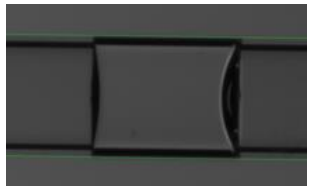
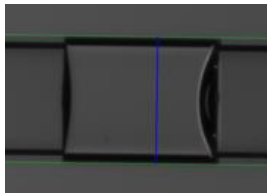
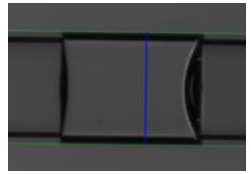
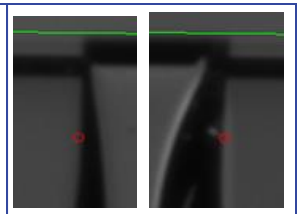
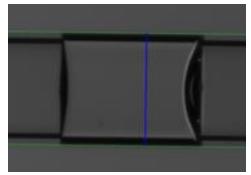
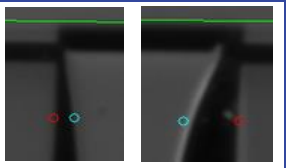
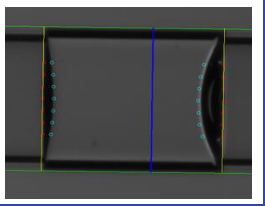
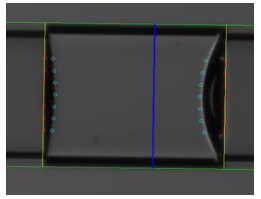
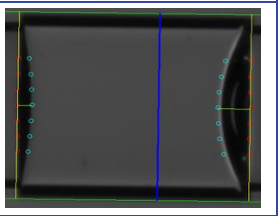
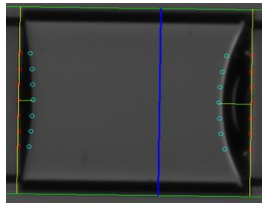
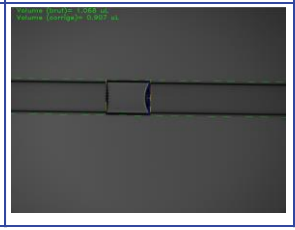
STEP 3
Imaging of the micro-volume (1 µl)



STEP 4

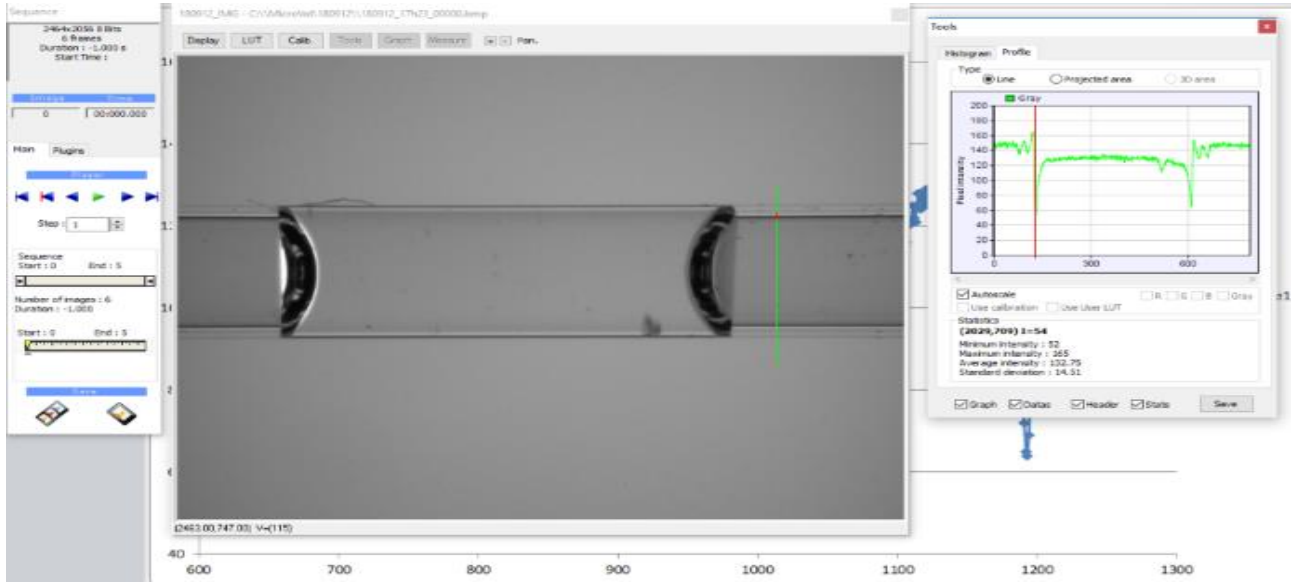
Measurement of the micro-volume

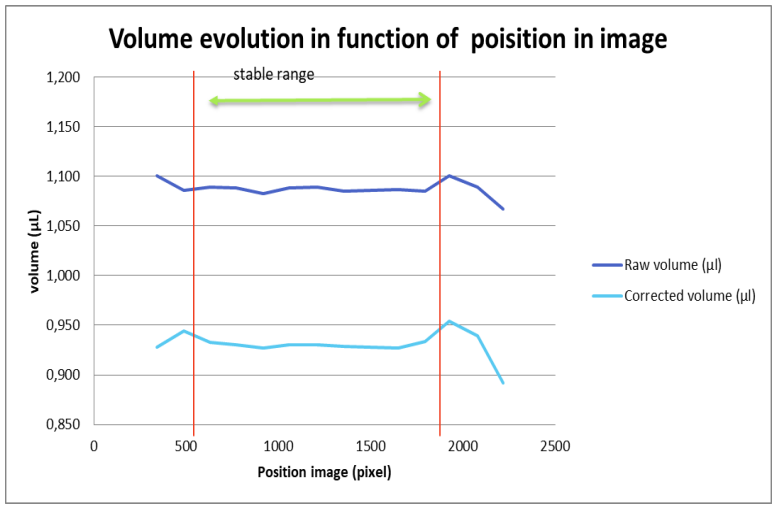
Step	Description	Input	Output
Edge detection	Oriented gradient calculation to detect horizontal borders		
Lines extraction	sharpening and detection hough line		
External edges extraction	external drop edges detection		
Spatial calibration	Minimum distance between borders calculation Zoom factor calculation relative to external diameter		

Vertical edges detection	Scan through image height to find left and right edges		
Internal edges detection	Scan through image height to find left and right edges		
External edges fitting	Linear fit on edges and minimum distance between lines calculation		
Meniscus height detection	Circular fit of internal points Finding maximum distance between edges and cirles Calculation of local radius		
Volumes calculation	Raw volume calculation : $Vb = \pi * r^2 * D$ Spherical edges calculation $Vcn = 1/6 * \pi * Hn * (3An^2 + Hn^2)$ Corrected volume calculation $Vc = Vb - Vc1 - Vc2$		

Results: comparison optical vs gravimetric methods

Capillary inner diameter (mm)	Position in image (pixel)	raw volume (µl)	corrected volume (µl)
1	340	1,101	0,928
1	485	1,086	0,944
1	628	1,089	0,933
1	771	1,088	0,930
1	916	1,083	0,927
1	1057	1,088	0,930
1	1210	1,089	0,930
1	1355	1,085	0,929
1	1496	1,086	0,928
1	1646	1,087	0,927
1	1792	1,085	0,934
1	1923	1,101	0,954
1	2078	1,089	0,939
1	2216	1,067	0,892





Capillary inner diameter	Mean corrected volume	Error optical vs gravimetric	Repeatability
1 mm	930 µl	0.2 %	0.3 %
0.5 mm	199 µl	0.4 %	0.5 %

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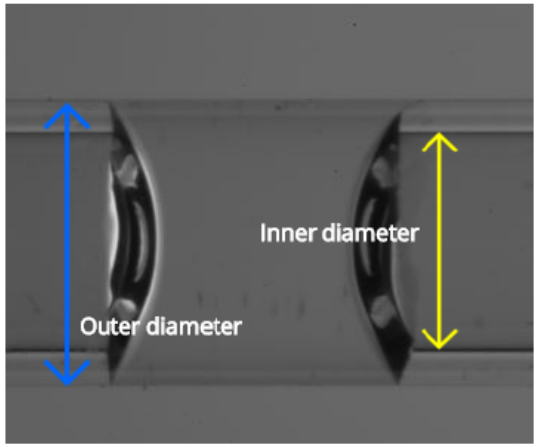
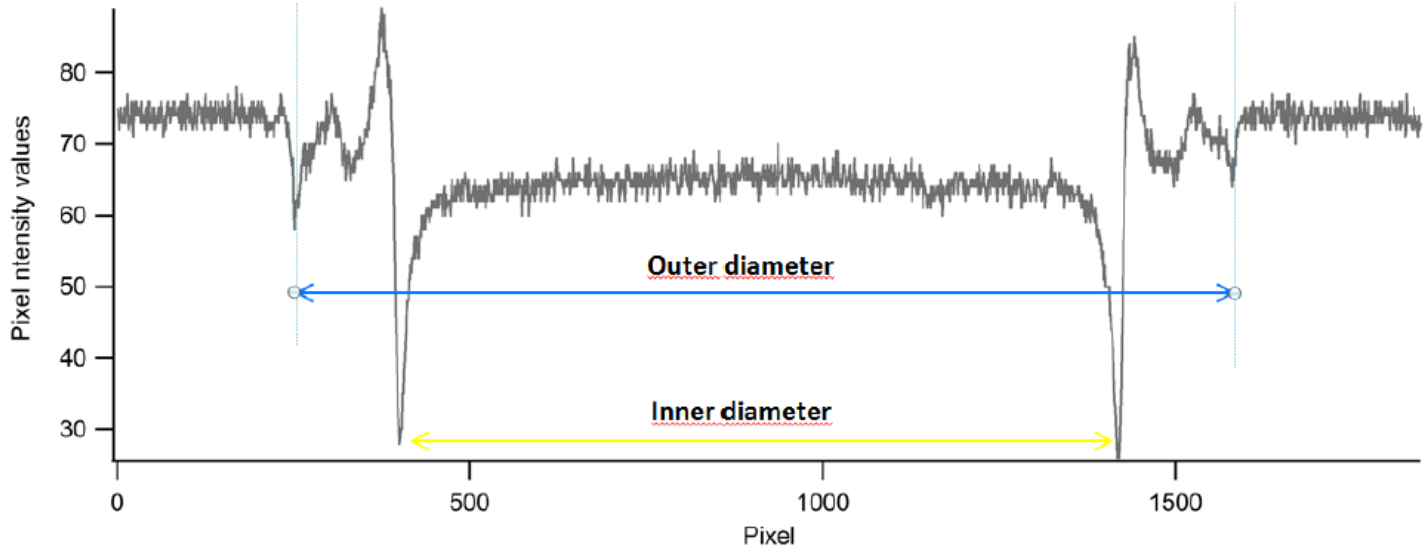
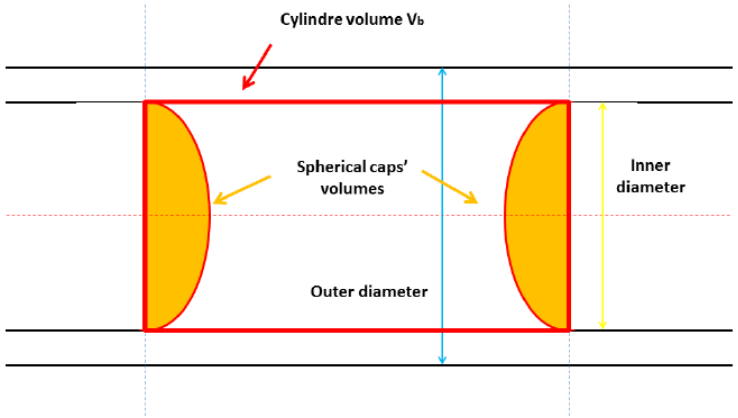
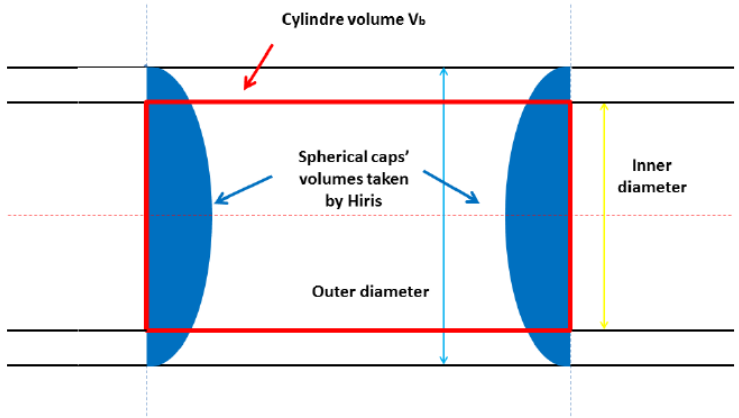
Uncertainty components: optical distortions

- Difference in refractive indexes: menisci diameter distortion



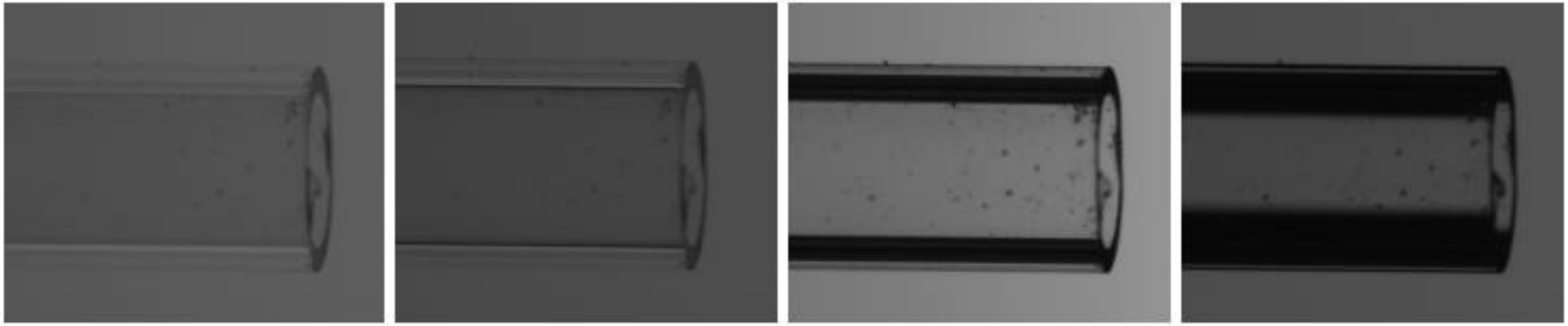






Uncertainty components: inner diameter measurement

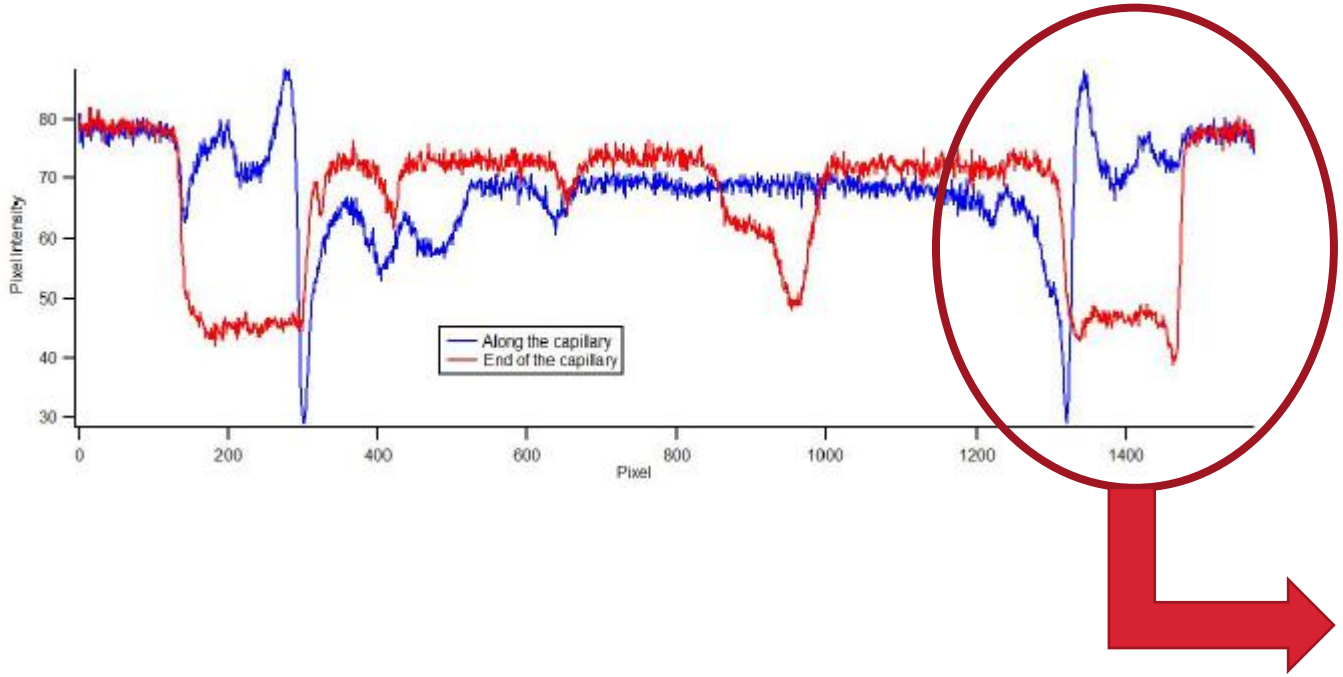
- Light conditions influence inner diameter contrast

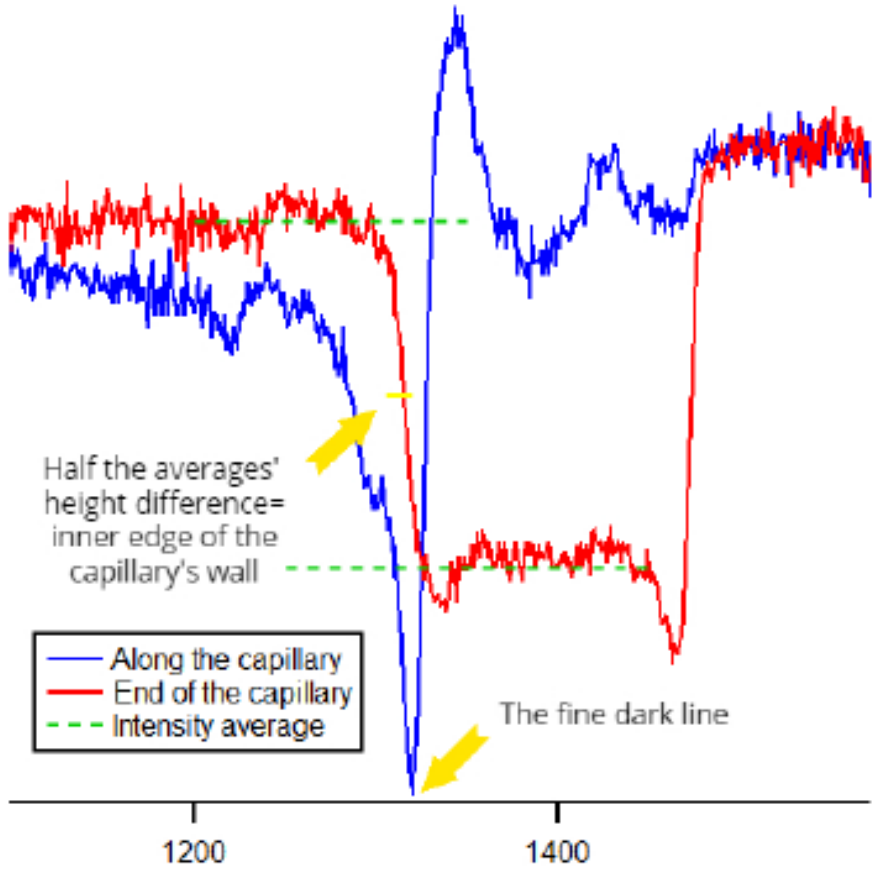


Distance from the light source increases from left to right

Uncertainty components: inner diameter measurement

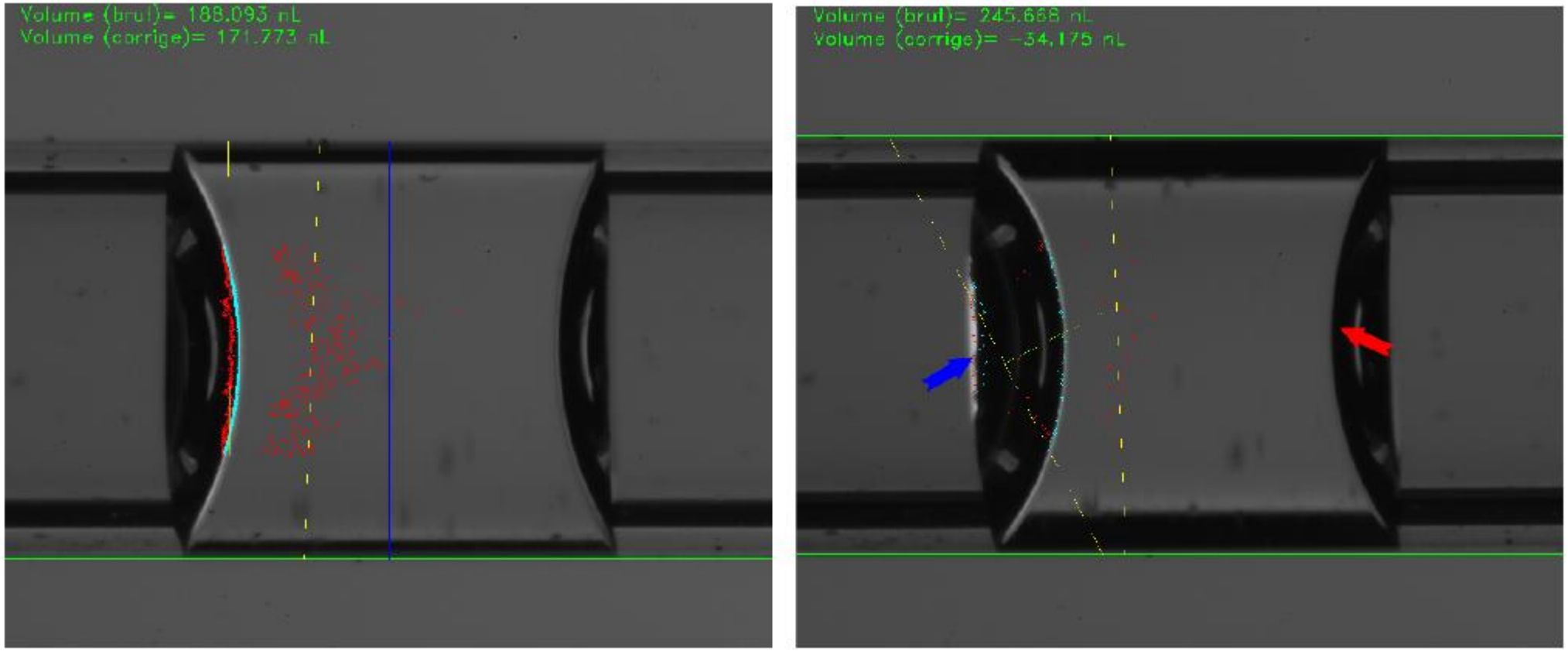
- Inner diameter measurement from intensity profile





Uncertainty components: menisci volumes

- Light conditions influence menisci edges detection



Poor light condition causes wrong menisci edges detection

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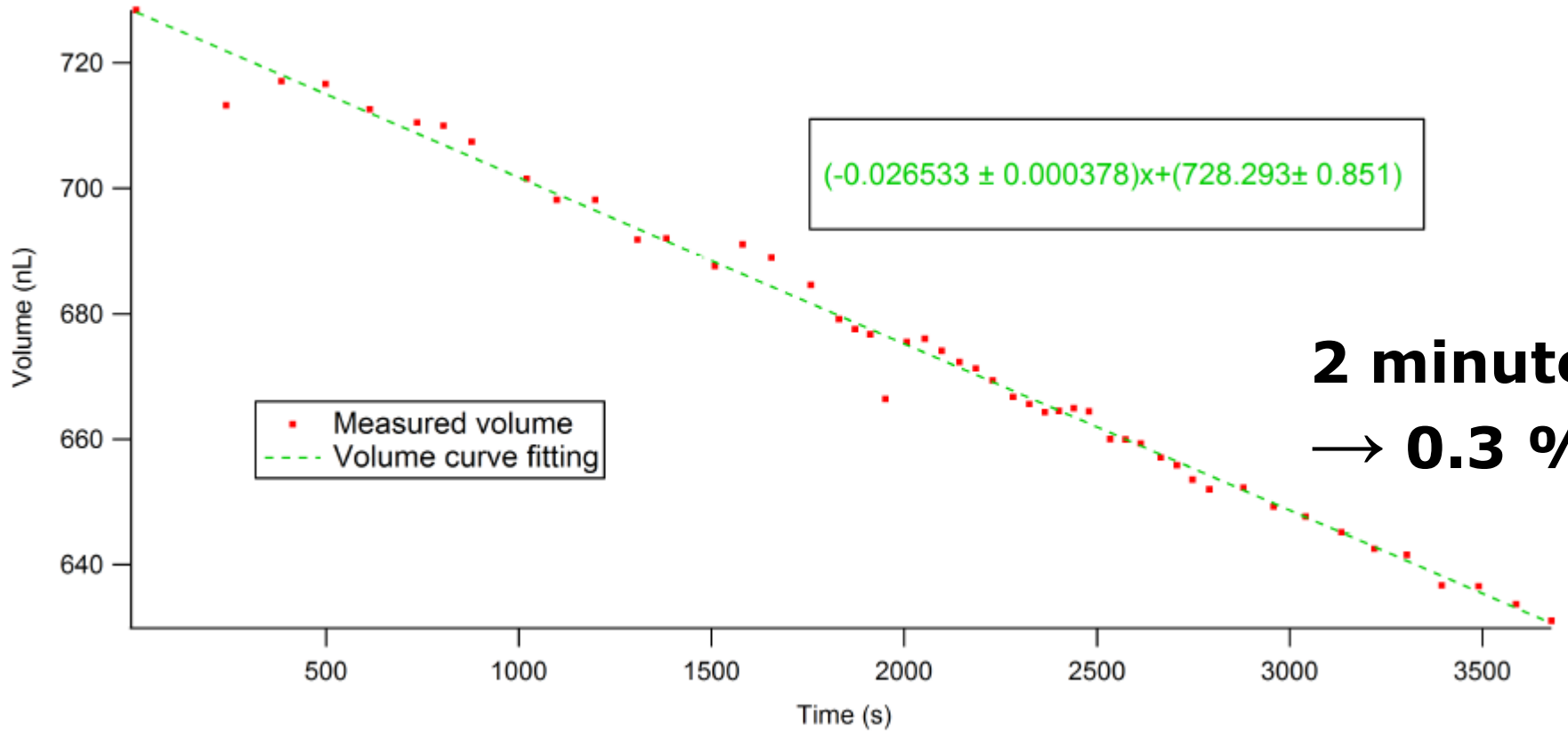
Uncertainty components: evaporation

- Microvolume's evaporation in the capillary between sampling and photograph, can be corrected



2 minutes = 3 nL

⟶ 0.3 % of 1 µl

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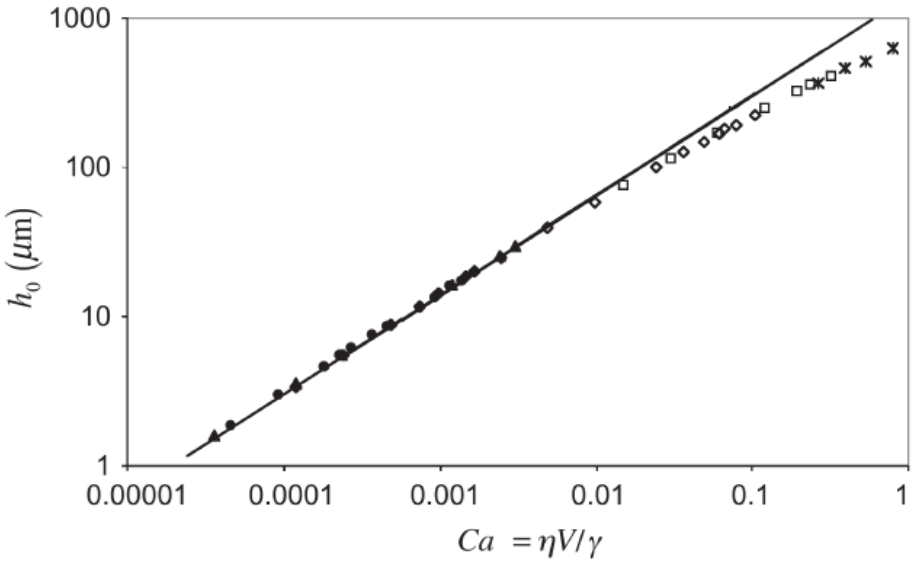
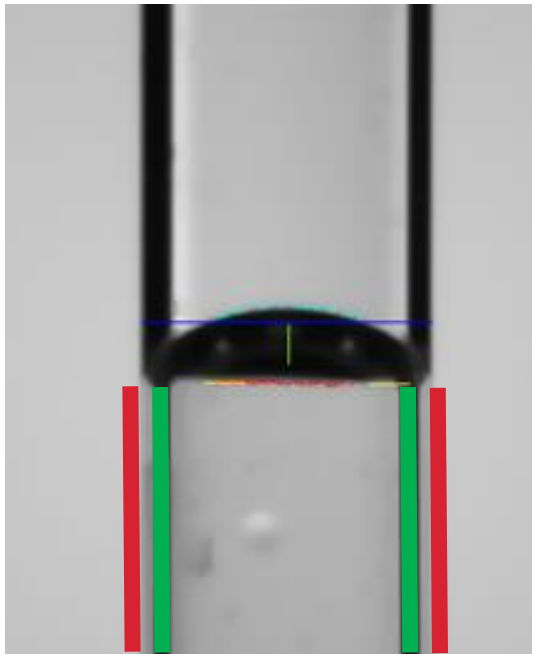
Uncertainty components: Landau-Levich film

- When the **volume is translated inside the capillary**, and when the **capillary is withdrawn from the vial**, a « Landau-Levich » **film of liquid** of thickness h_0 **can adhere** to the **inner** and **outer** surface of the capillary



- **Theory:** thickness depends on sampling speed, surface tension and liquid viscosity
- **Experiments** show that in our case the **film thickness is smaller than the imaging system resolution (< 1µm)**



→ **V_{film}< 0.2 % of a 1 µl sampled volume translated at 1 mm from the capillary end**

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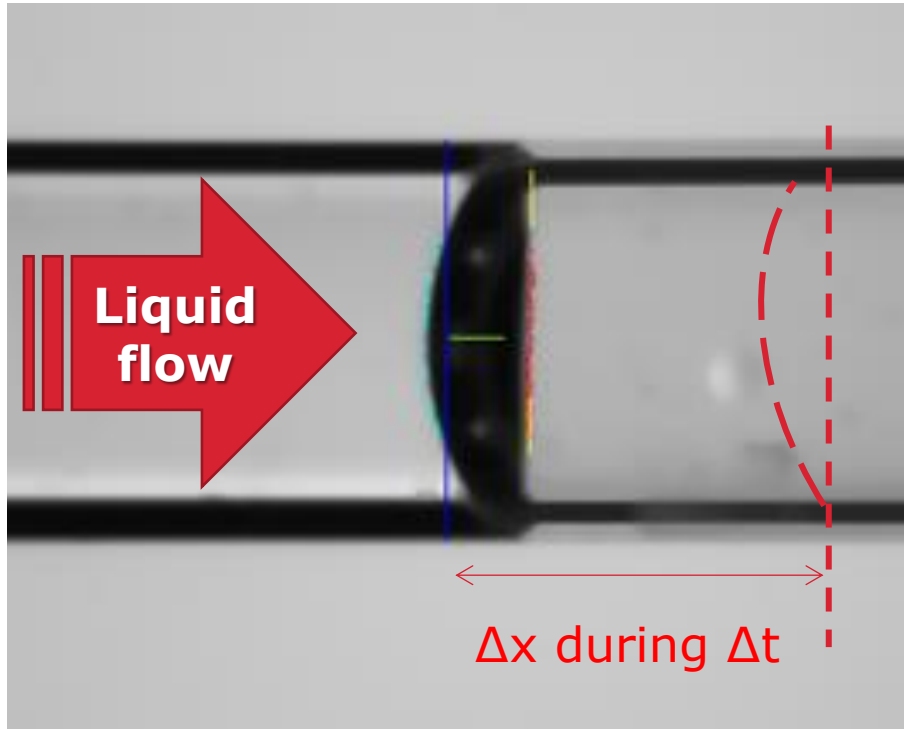
Future developments: nano-flow rates measurements

Based on the same system, just measure menisci position:



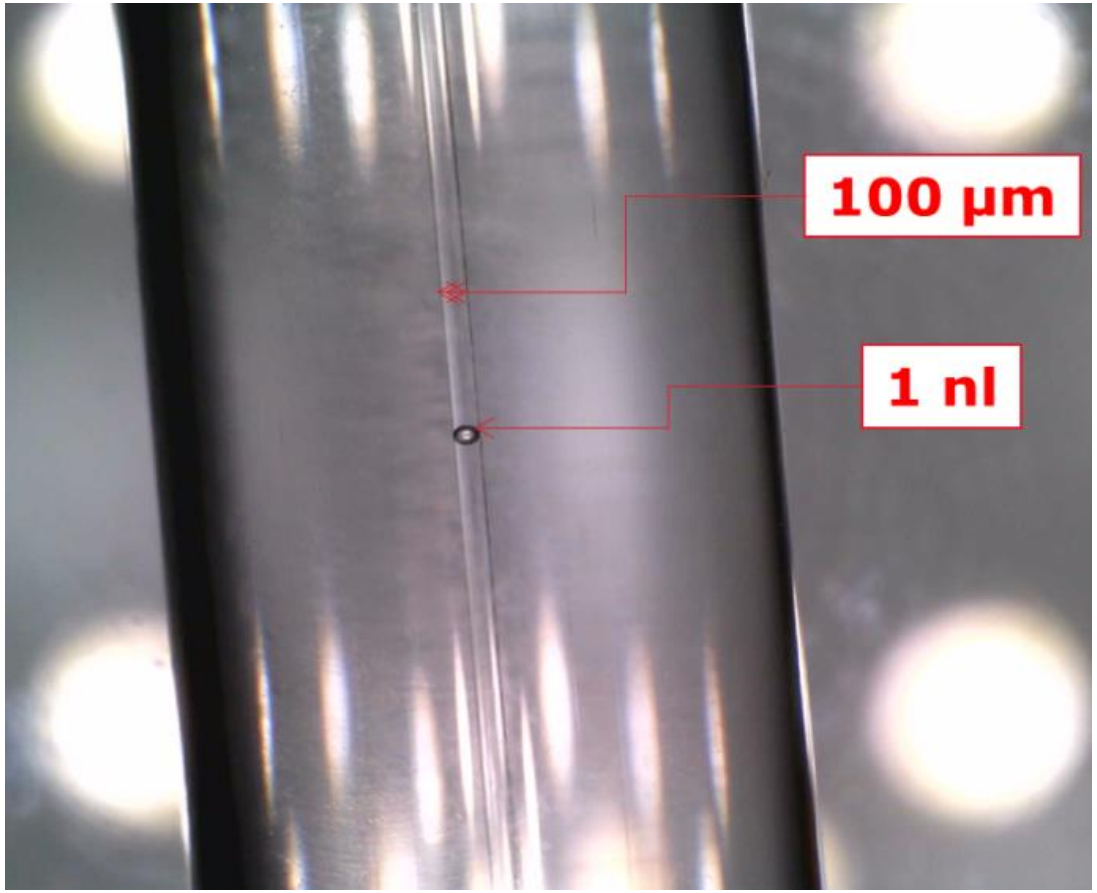
$$Q_v = \frac{\pi . r^2 . \Delta x}{\Delta t}$$

- Choose capillary diameter adequately given the flow rate range to be measured
- **Compromise** between **capillary diameter** (bigger uncertainty for smaller diameter) and **flow speed/rate** (distance and time interval between two successive pictures) and **evaporation rate** given capillary diameter

Future developments: nano-flow rates measurements

- First tests at LNE-CETIAT from 1 $g.h^{-1}$ down to 1 $nl.h^{-1}$
- Results to be published next year, in the scope of JRP MeDD2

Pictures of 1 nl volume in a capillary, using CETIAT's system:



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Conclusion

- Optical prototype system for calibration of radiopharmaceuticals sampled microvolumes
- Validated against gravimetric method, for 1 µl to 200 nl sampled volumes
- Uncertainty components evaluated experimentally, combination expected to be within U = 1 % (k=2)
- Extension to nano-flow rates measurement using the same system, in 2020 in the scope of EURAMET EMPIR JRP « Metrology for Drug Delivery II »

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