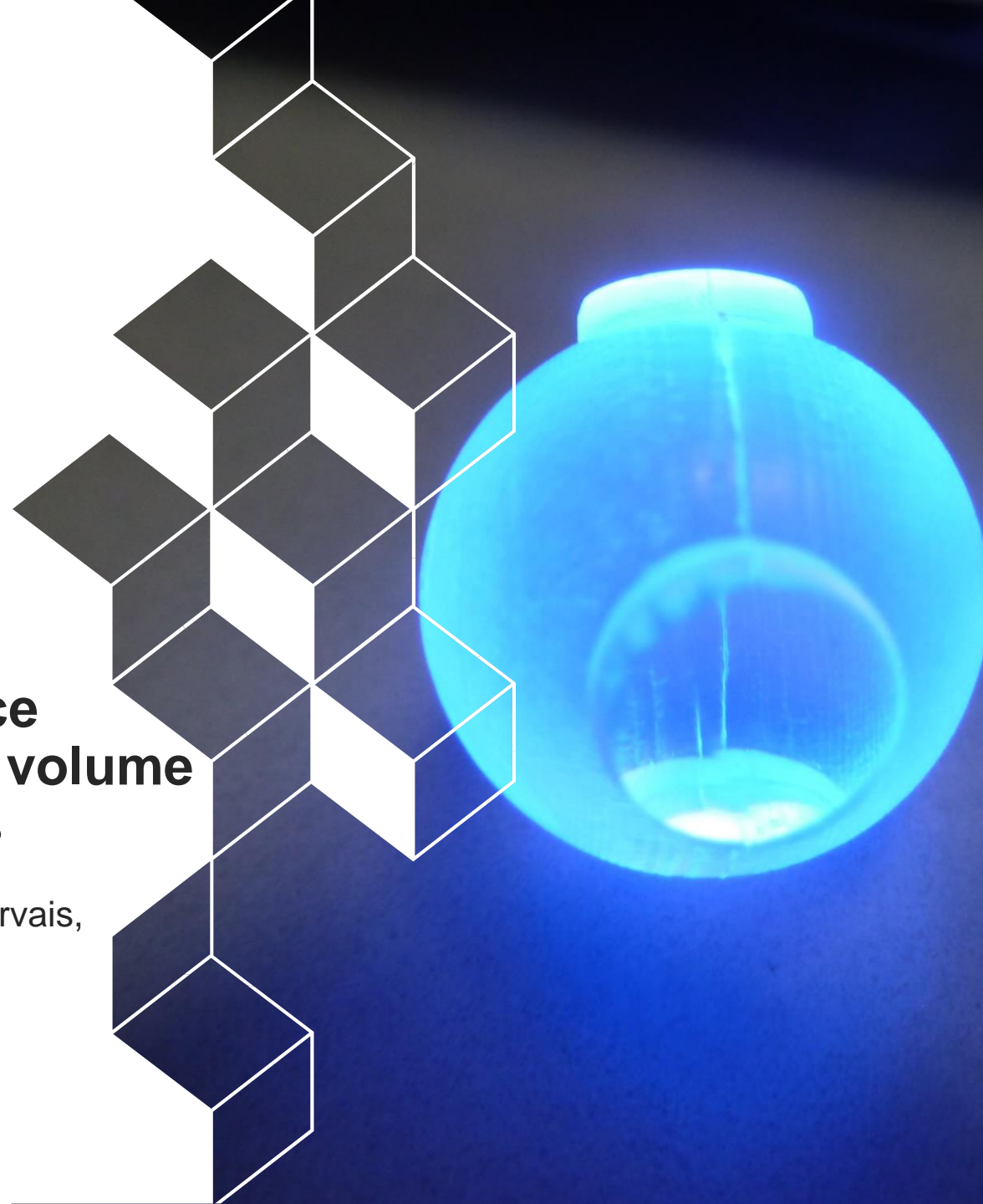




Development of a portable device for primary measurement of the volume activity of radiopharmaceuticals

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Project concept and needs

Needs:

Before injection of radiopharmaceutical, activity measurement by calibrated dose calibrators

Several radionuclides used: ^{131}I , ^{67}Ga , $^{99\text{m}}\text{Tc}$, ^{18}F , ^{11}C , ^{15}O , ...

Conventional logistics for calibration difficult to apply (transportation, distance from production laboratory, radiation protection, authorizations)

Objectives:

- To propose a first idea of a functional device to allow the future measurement directly at the output of the cyclotron
 - To develop a reference measurement system for *in-situ* calibration for radionuclides used in PET imaging using the Triple to Double Coincidence Ratio method;
 - Short-lived β^+ emitting radionuclides : example ^{11}C ($T_{1/2} = 20.4$ min) and ^{15}O ($T_{1/2} = 2$ min)

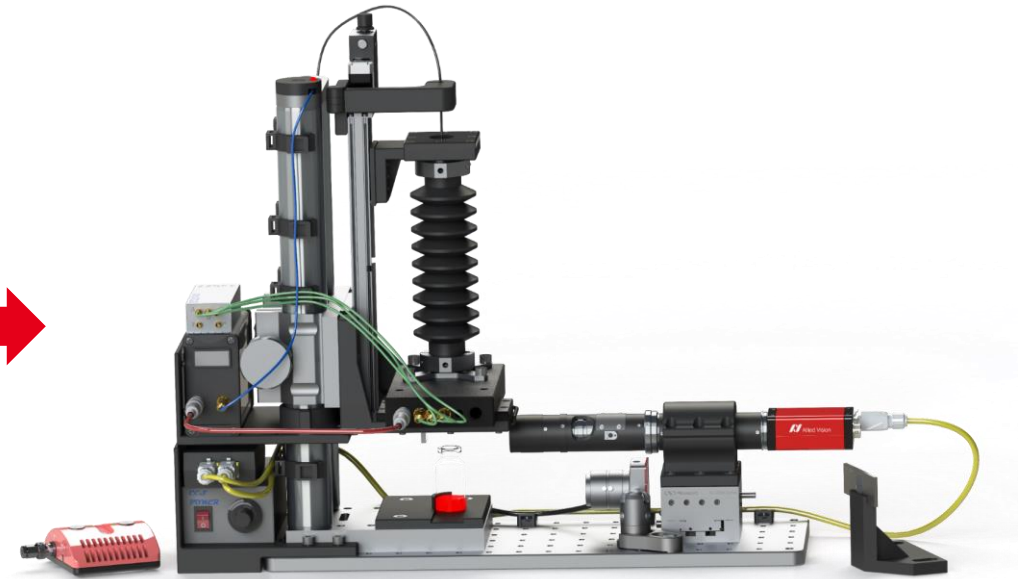
A first portable device with limits

Main interest of a portable TDCR measurement device: *in-situ* measurement

- Huge and non-transportable laboratory measurement device: problem for short-lived radionuclides



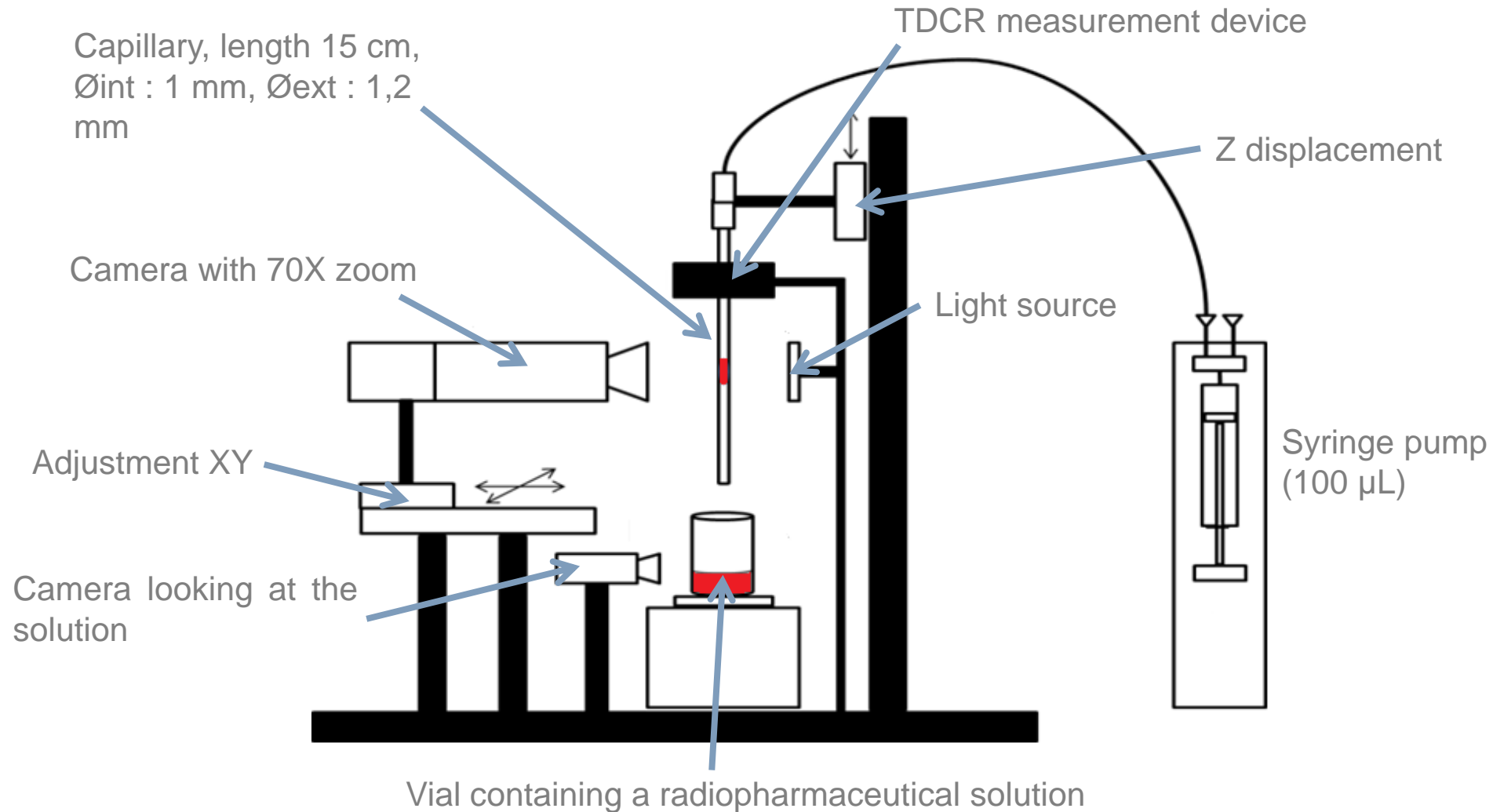
B. Sabot, *et al.*, 2022, Performance of portable TDCR systems developed at LNE-LNHB, NIMA 1034



- Working device but limited:
 - Typical activity: some hundred of kBq
 - Liquid scintillation source preparation

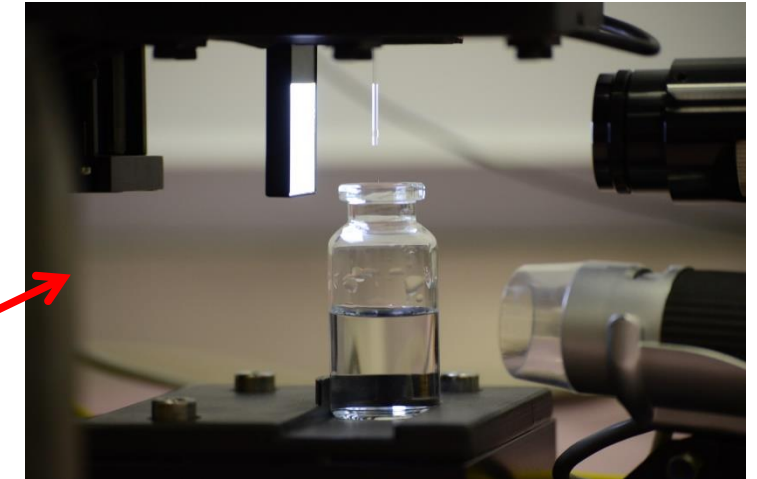
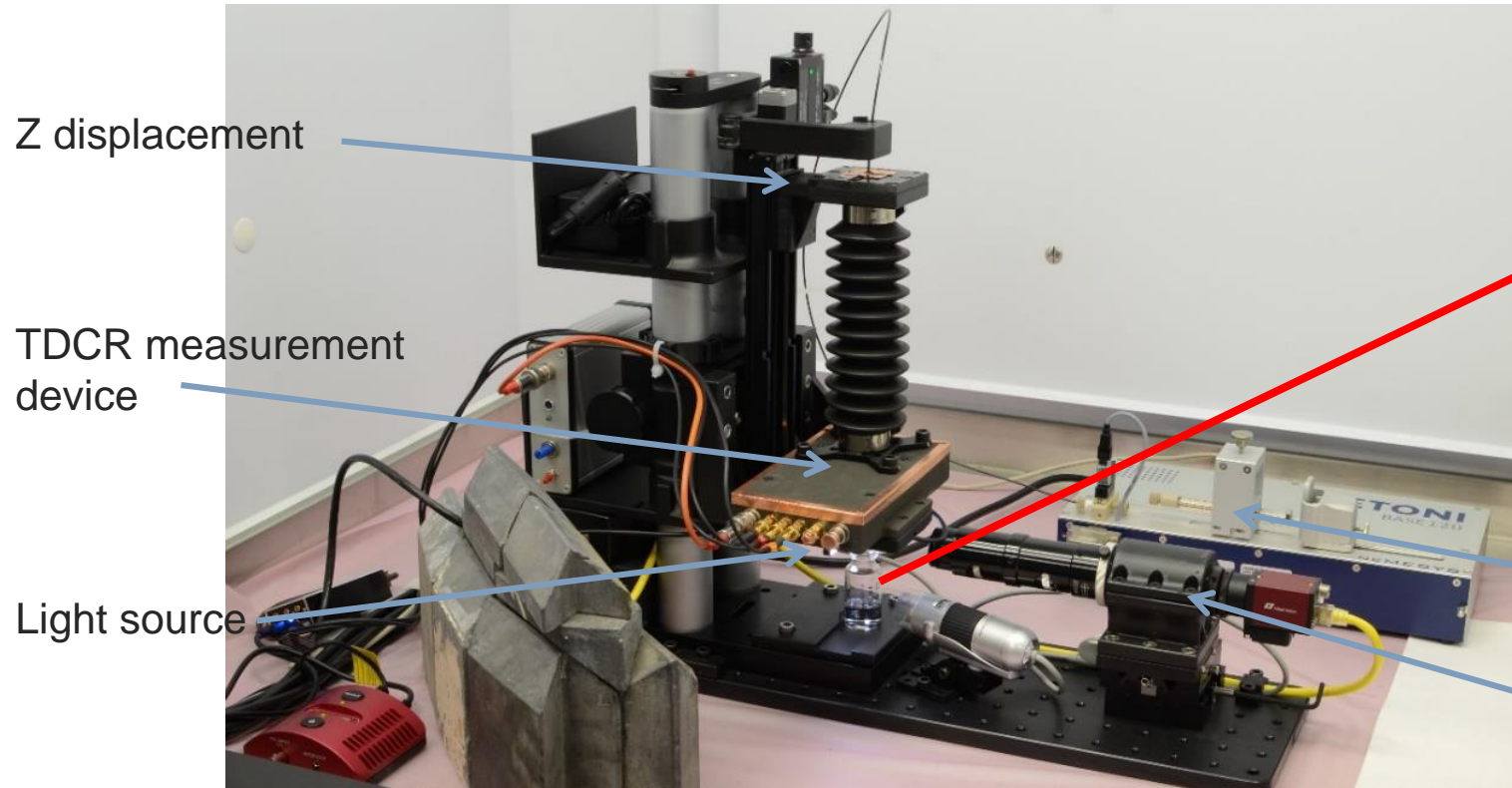
- Solution presented here for MBq·mL⁻¹:
 - Sampling and volume measurement
 - Activity measurement

Principle (Presented at ICRM-2019)



The complete measuring device is compact and transportable

Designed to allow secure capillary movement and light tightness of the system



Vial containing a radiopharmaceutical solution

Syringe pump (100 μ L)

Camera with 70X zoom + volume measurement analysis done with LNE-CETIAT method on HIRIS software (meniscus and drop identification)

Measurement device in place at Orsay Hospital (CEA/SHFJ)

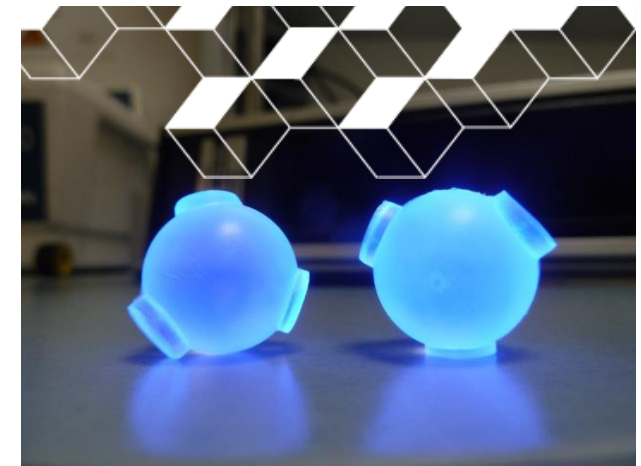
Detection module

Solid organic scintillator with TDCR detection system

- Design and manufacture of the RCTD device by 3D printing
- Design and manufacture of the scintillator
 - Mold designed by CAD for optimization of shape, yield and fabrication
 - Manufacture of the scintillator by CEA: possibility to adapt the mixture according to the needs, well known type of scintillator (stable in time, resistant to high doses)

Scintillator with holes for the passage of the capillary

3 PMTs

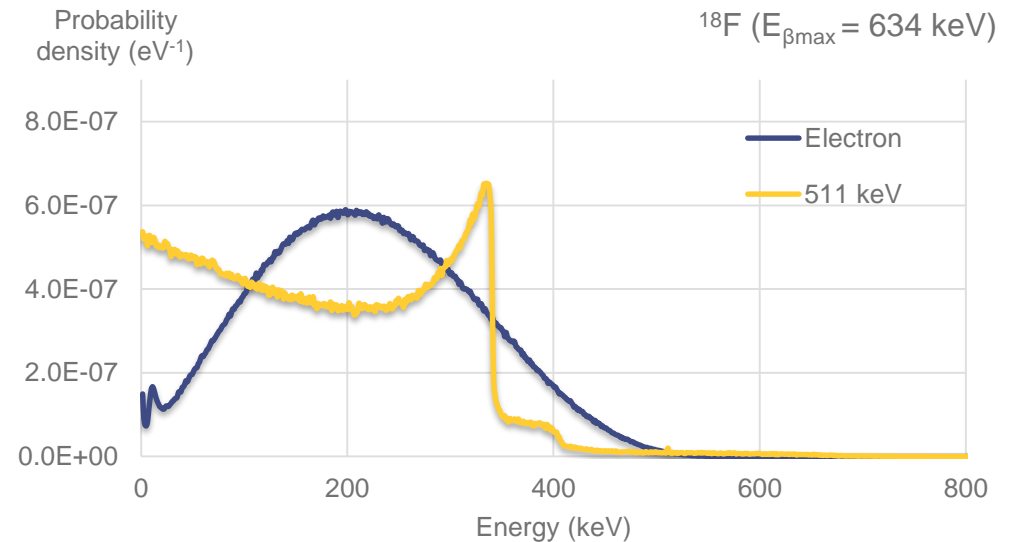
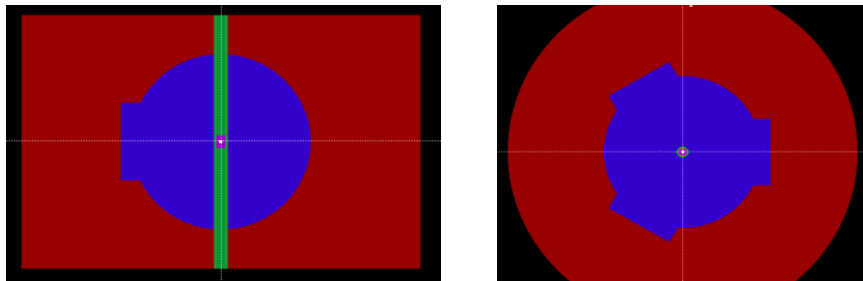


Method

TDCR method with absorbed spectrum by scintillator $S(E)$ calculated by simulation

$$RCTD = \frac{\int_{spectre} S(E) (1 - e^{-\frac{\nu\alpha m(E)}{3}})^3}{\int_{spectre} S(E) (3(1 - e^{-\frac{\nu\alpha m(E)}{3}})^2 - 2(1 - e^{-\frac{\nu\alpha m(E)}{3}}))^3} \text{ with } m(E) = \int_0^E \frac{dE}{1 + k_B \frac{dE}{dx}}, \quad TDCR = \frac{T_{exp}}{D_{exp}} \approx \frac{\epsilon_T}{\epsilon_D}$$

- Monte-Carlo PENELOPE 2018 adapted according to the measured RN, the drop dimension, the capillary and scintillator type



- Concept: maximize the detection efficiency to reduce model dependency and thus size of the sample

In-situ tests - Protocol

The *in-situ* tests were performed at the Orsay hospital (CEA/DRF/JOLIOT/SHFJ/BIOMAPS)

- Measurement of residuals of solutions ready for injection of ^{18}F and ^{11}C
- After each sampling of a drop of solution by the capillary, the mother solution is poured into a vial in a lead shielding (impact on the counting experimentally verified)
- After the volumetric activity measurement, ejection of the drop into a liquid scintillation vial for comparison using the validated portable micro-TDCR device

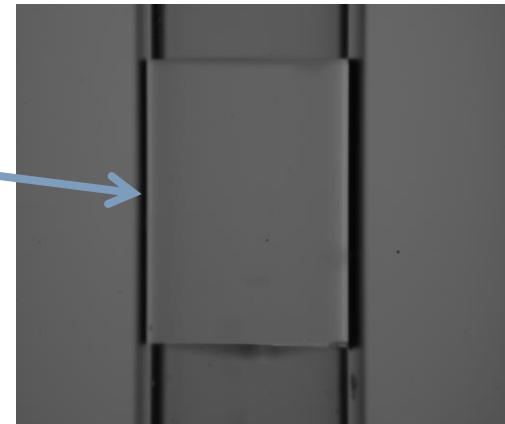
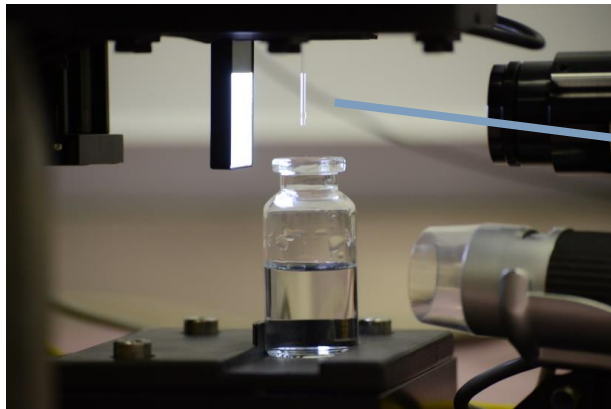


- Processing of all results after the test campaign

In-situ tests - Problem

Drop ejection tests

- On the advice of LNE-CETIAT, treatment of the capillary in order to:
 - Avoid spreading the solution over the capillary
 - Encourage the ejection of the drop



- Consequences:
 - Complete ejection of the drop without counting residue when measuring the capillary
 - Disappearance of the meniscus simplifying the volume calculation



A problem?
The solution

In-situ tests - ^{18}F

After characterizing the device, two comparisons were made:

- First test with a vial of ^{18}F FDG, colloidal solution of fluorodesoxyglucose is physiological serum
 - Decay scheme with 3% electron capture
 - β^+ max energy of 634 keV
- Two vial samples tested

Vial number	Volumic activity capillary device (MBq·ml ⁻¹)	Relative standard uncertainty (%)	Volumic activity micro-RCTD (MBq·ml ⁻¹)	Relative standard uncertainty (%)	Difference	Measurement time	Remainder after transfer between the two methods	Observation on the drop
1	79.3	1.9	82.3	1.2	- 3.7%	10 x 30 s	Yes ~ 0.3%	-
2	75.2	2.7	75.2	2.3	0.01%	10 x 30 s	No	-
2	80.1	3.4	74.9	3.6	6.6%	20 x 60 s	No	-25% volume and drop moved in capillary after 22 min
2	85.0	4.4	78.5	4.3	7.6%	10 x 60 s	No	Drop size too small

} After Rain-X

In-situ tests - ^{11}C

After characterizing the device, two comparisons were made:

- Tests on a vial of [^{11}C]PIB, Pittsburgh Compound B in colloidal solution of physiological serum and 10%w of ethanol
 - Simpler decay scheme than ^{18}F
 - β^+ max energy of 960.5 keV
- Lower impact of the spectrum on the measurement parameters
- Only one measurement was possible due to the period and timing of the tests

Vial number	Volumic activity capillary device (MBq·ml ⁻¹)	Relative standard uncertainty (%)	Volumic activity micro-RCTD (MBq·ml ⁻¹)	Relative standard uncertainty (%)	Difference	Measurement time	Remainder after transfer between the two methods
1	9.53	1.4	9.47	1.1%	0.61%	5 x 60 s	No

In-situ tests - Observations

Observation on results:

- First tests of the device in real conditions:
 - Impact of disturbing activities in the laboratory (production of radionuclides); **can be easily mitigated**
 - Test on a real solution: sampling, ejection of the drop, conditioning of the user; **sampling can easily be done fast even if not automatized for now**
 - Effect of evaporation of the drop because of too long measurement:
 - high impact on the detection efficiency; **short measurement is exactly what we need and can mitigate this factor**
 - the displacement of the drop was observed on the third experiments; **leak in the tubing from the sampler was mitigated using stainless steel tube**
- The dose was limited for the operator to 2.4 μSv on 1 week of experiments with vial manipulation

Uncertainty budget on the measurement of volume activity



COMPONENT	RELATIVE STANDARD UNCERTAINTY		EVALUATION METHOD
	¹⁸ F	¹¹ C	
Coincidence window	0.07%	0.04%	Comes from the standard deviation of the results obtained for different coincidence windows
Dead time	0.12%	0.03%	Comes from the standard deviation of the results obtained for different dead time windows
Statistic	0.05%	0.09%	Count rate D uncertainty
Blank	0.06%	0.01%	Uncertainty in the measurement of blank
Time	0.3%	0.17%	Uncertainty of 1 s on the acquisition time
Spectra	0.1%	0.01%	Impact of the spectrum shape on the simulations; mainly related to the uncertainty on the Qvalue used in BetaShape 2.0 (Mougeot, 2015)
Nuclide data	0.2%	0.01%	Uncertainty on emission intensities and electronic capture (source DDEP)
S(E)	1.4%	1.1%	Obtained from simulations with a difference of 20 µm on the diameter and 20 µm on the height of the drop; normal distribution (conservative compared to volume measurement uncertainty)
Accidental coincidences	0.03%	0.03%	Corresponds directly to the applied correction factor (very conservative)
Correction factor during measurement	0.002%	0.002%	Uncertainty due to decay correction during measurement (low because of fast measurement)
Correction factor reference date	0.004%	0.03%	Uncertainty related to the decay correction to bring the result back to the same reference date
Volume	1.1%	0.9%	Uncertainty related to the volume given by LNE-CETIAT in the case of a drop with 2 meniscus
ACTIVITY	1.5%	1.1%	Relative standard uncertainty on the measured activity
VOLUMIC ACTIVITY	1.8%	1.5%	Relative standard uncertainty on the measured volumic activity

The main uncertainty component corresponds to the simulations including the variation of position, size and composition of the drop and capillary

Summary

Development of a volume activity measurement instrument for *in-situ* calibration of short-lived radiopharmaceuticals used for PET imaging, volume activity measurement with a relative standard uncertainty < 2%.

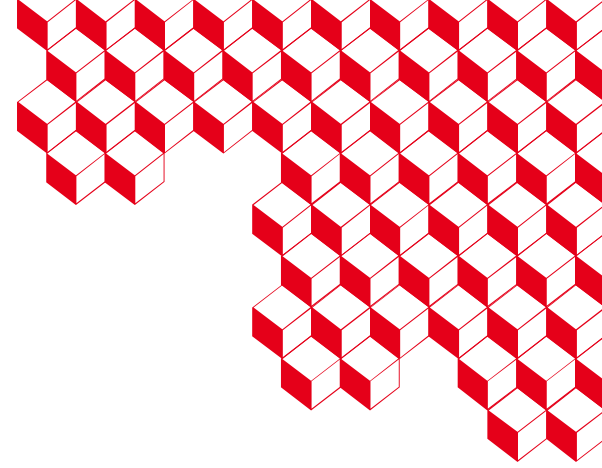
Semi-automated system and fast measurement is needed: total 300 s (volume measurement and offline activity calculation)

Possibility of measuring very high levels of volume activity: several hundreds MBq·mL⁻¹

First comparisons of measurements *in-situ*: ¹⁸F, ¹¹C

The device can be adapted to other radionuclides: this will depend on the type of emission / intensity / energy...

Next steps: improvement of the device with smaller volume, inorganic scintillator, gamma spectrometry for impurity; goal GBq·mL⁻¹ for on-site and operando radiopharmaceutical production quality control



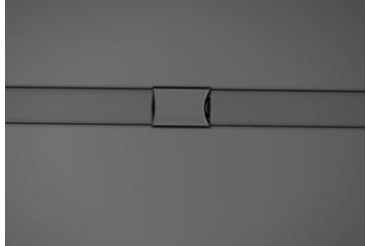
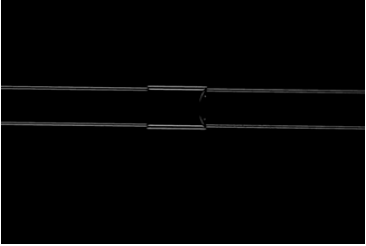
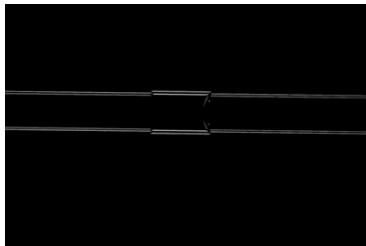
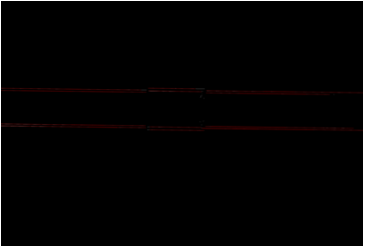
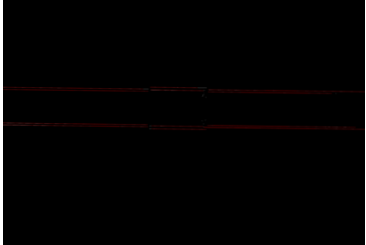


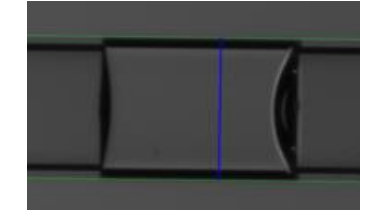
Thank you

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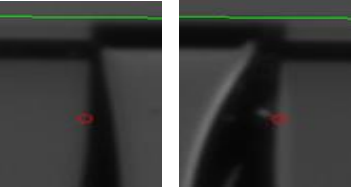

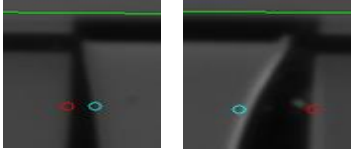




CEA, Centre de Saclay

LNE-CETIAT volume measurement

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		

LNE-CETIAT volume measurement



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 circles Calculation of local radius		
Volumes calculation	Raw volume calculation : $V_b = \pi \cdot r^2 \cdot D$ Spherical edges calculation $V_{cn} = \frac{1}{6} \cdot \pi \cdot H_n \cdot (3A_n^2 + H_n^2)$ Corrected volume calculation $V_c = V_b - V_{c1} - V_{c2}$	