UNIVERSITÀ DEGLI STUDI DI MILANO
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Online monitoring for column separation of ^{177}Lu from enriched ^{176}Yb irradiated target

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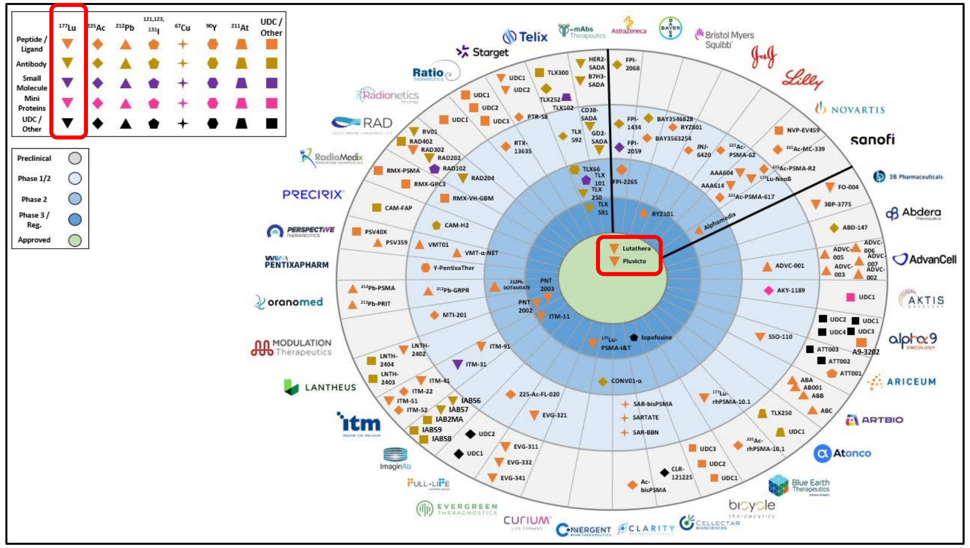
ISOTOPIC TIME MACHINE
FROM CULTURAL HERIRAGE TO SUSTAINABLE FUTURE

FLORENCE 15-19 FEB 2026
ICI 2026
12TH INTERNATIONAL CONFERENCE ON ISOTOPES

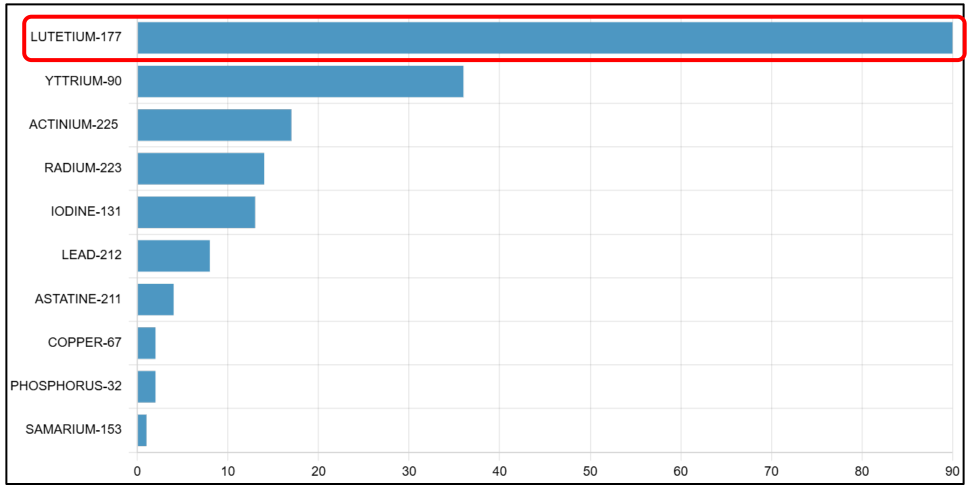
Background

- Lutetium-177 (177Lu) is a beta-emitting radionuclide. Its radiopharmaceuticals, such as Luthatera for neuroendocrine tumors and Pluvicto for prostate cancer, are approved and used worldwide.
- Among therapeutic radionuclides in ongoing clinical trials globally, 177Lu is the most widely used, accounting for approximately half of all trials.

Clinical Trial Status by Pharmaceutical Manufacturer



Number of clinical trials per radionuclide



https://www.theranostictrials.org/

Background

- For basic research, 177Lu must still be imported through the Japan Radioisotope Association in Japan. (JAEA is considering distribution)
- Domestic production of therapeutic nuclides is a critical element for sustainable radionuclide therapy, and 177Lu, whose clinical use is increasing, is the top priority.
- Novartis announced an expansion of its Sasayama plant facilities in Japan, but the raw material 177Lu must still be sourced from overseas production.
- There is a risk that treatment plans could be forced to halt due to unforeseen impacts such as conflicts or natural phenomena.

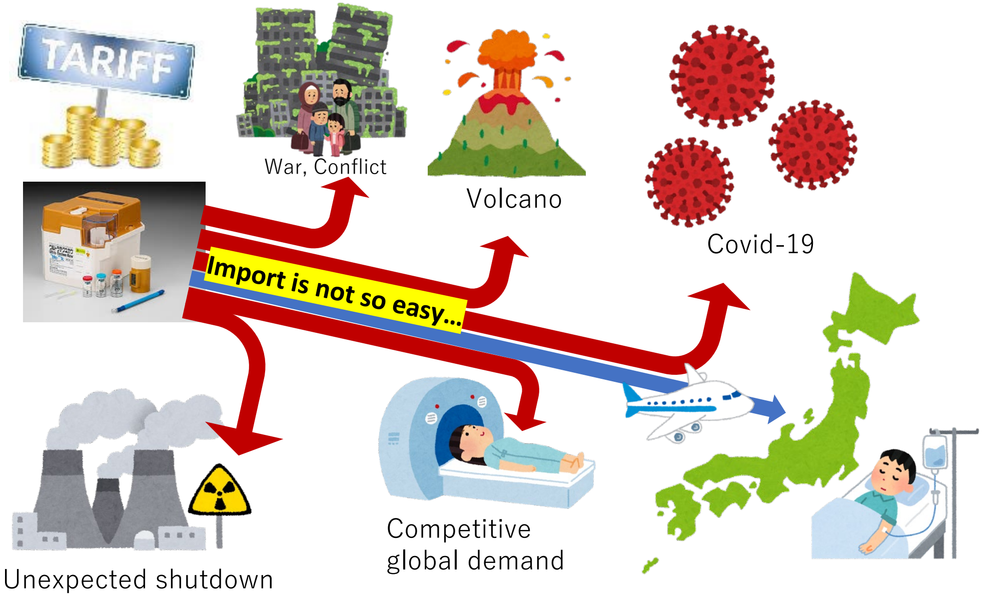

NIKKEI Asia

PHARMACEUTICALS

Novartis to mass produce next-generation cancer drugs in Japan

Swiss drugmaker plans to start making radiopharmaceuticals there in 2026

Novartis currently produces radiopharmaceuticals in Europe and the U.S. and exports them to Japan. (Novartis)



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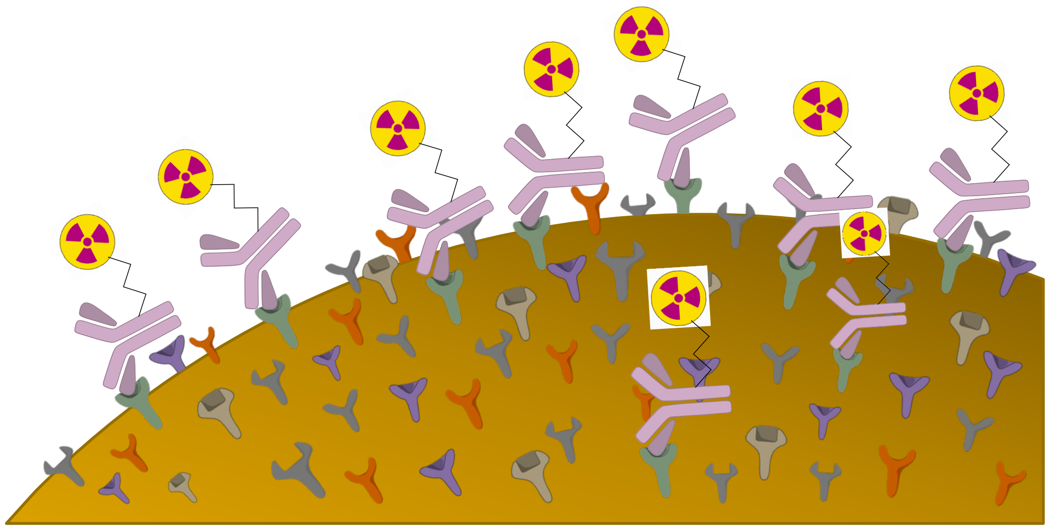
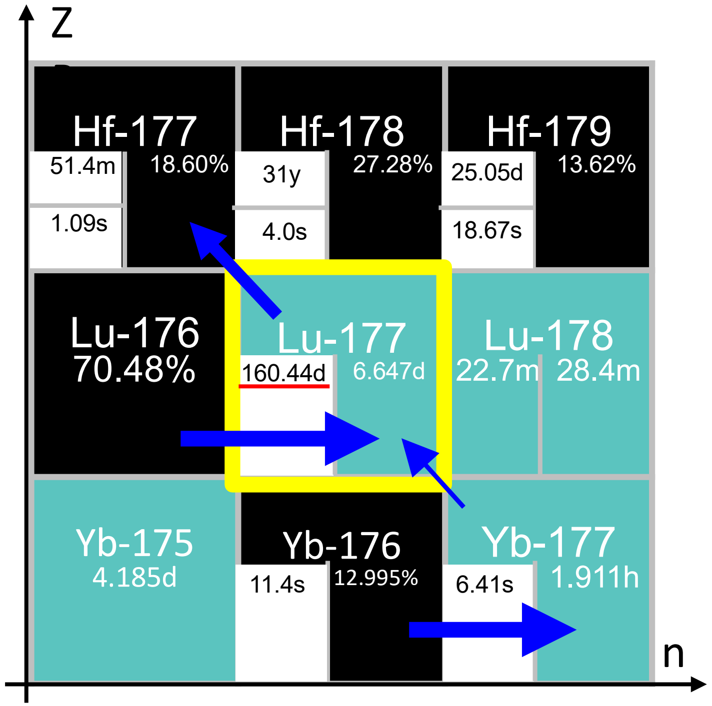
Production route

$^{176}Lu(n,\gamma)\,^{177}Lu,\ ^{177m}Lu$
$^{176}Yb(n,\gamma)\,^{177}Yb \xrightarrow{\beta^-} {}^{177}Lu$

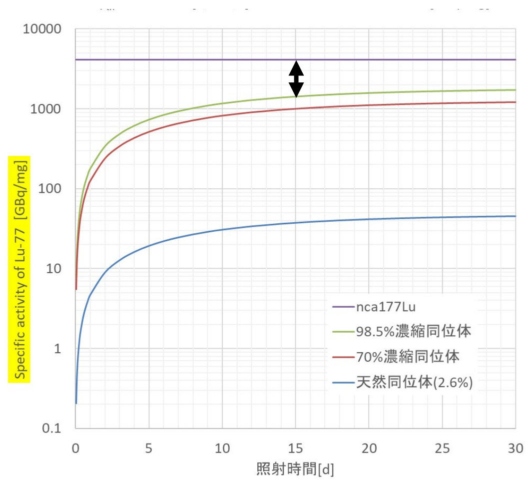




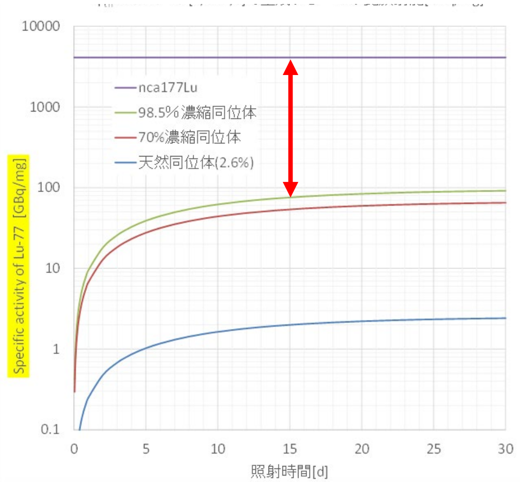
- Theoretical nca177Lu: 4,100 GBq/mg
- Commercial nca177Lu: > 3,000 GBq/mg

Irrad time & Specific Activity

MURR or BR2



KURR (Hyd) 1MW



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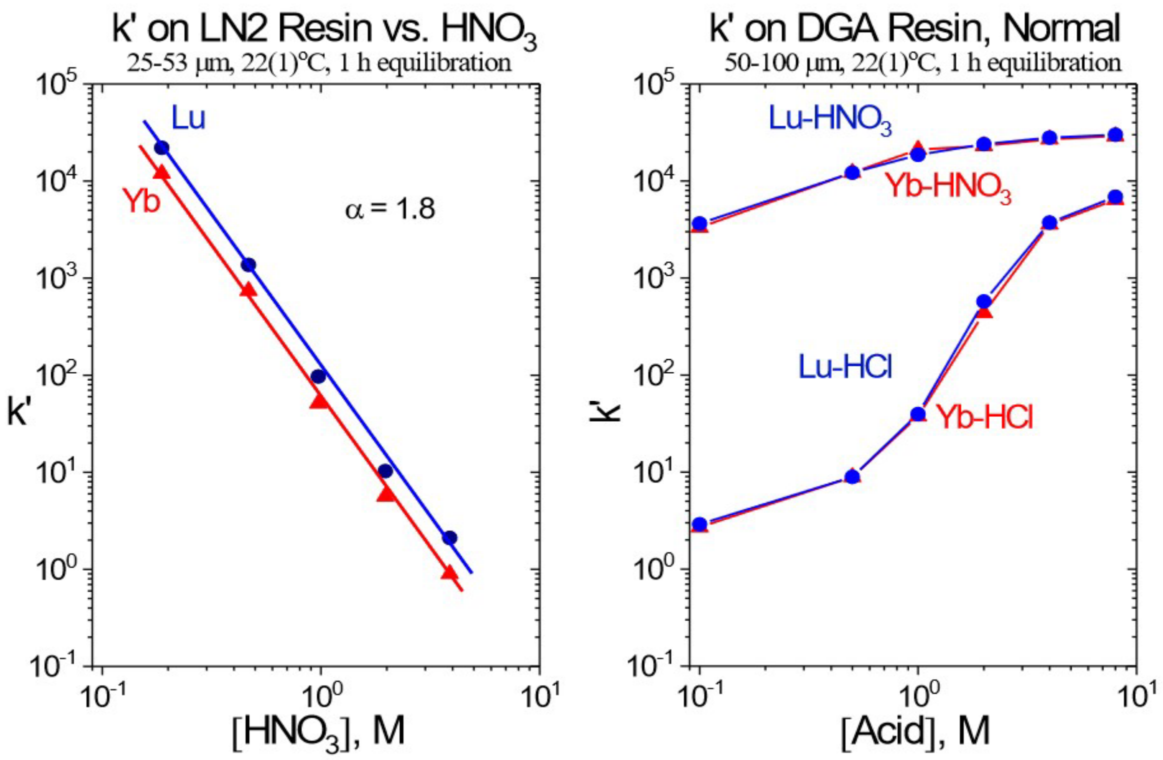
Lu-Yb Separation

- Extraction chromatography is a widely used technique for chemical separation of Ytterbium (Yb) and medically relevant Lutetium-177 (^{177}Lu)
- However, chemical similarity between Lu and Yb requires a larger column size and more eluent for gram-scale Yb target separation.
- It is essential to fully understand the process of separating Yb and Lu in the column and to extract only the required ^{177}Lu fraction to improve the efficiency of the chemical separation operation.



Horwitz, E.P. McAlister, D.R. Bond, A.H. Barrans, Jr., R.E. Williamson, J.M. 2005. A Process for the Separation of ^{177}Lu from Neutron Irradiated ^{176}Yb Targets, Applied Radiation and Isotopes, 63, 23-36.

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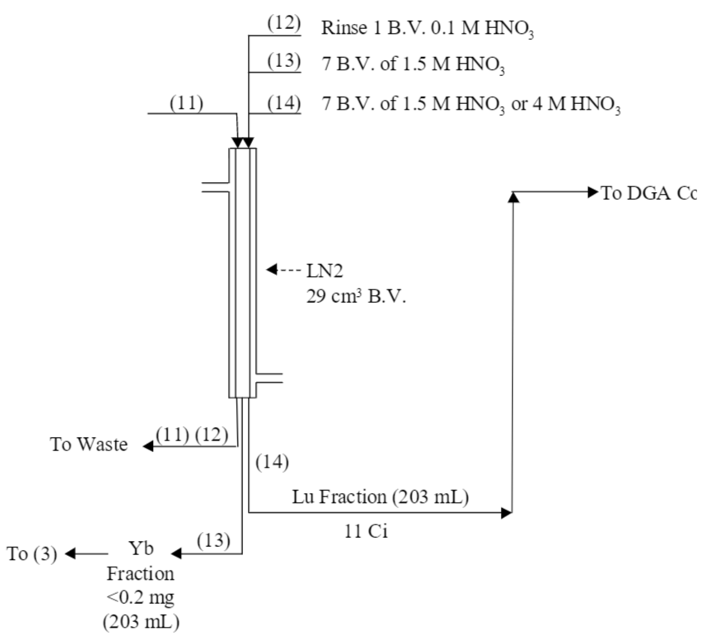


Figure 12. Conceptual flowsheet for the separation of ^{177}Lu from ^{176}Yb: Part C. Secondary Separation System

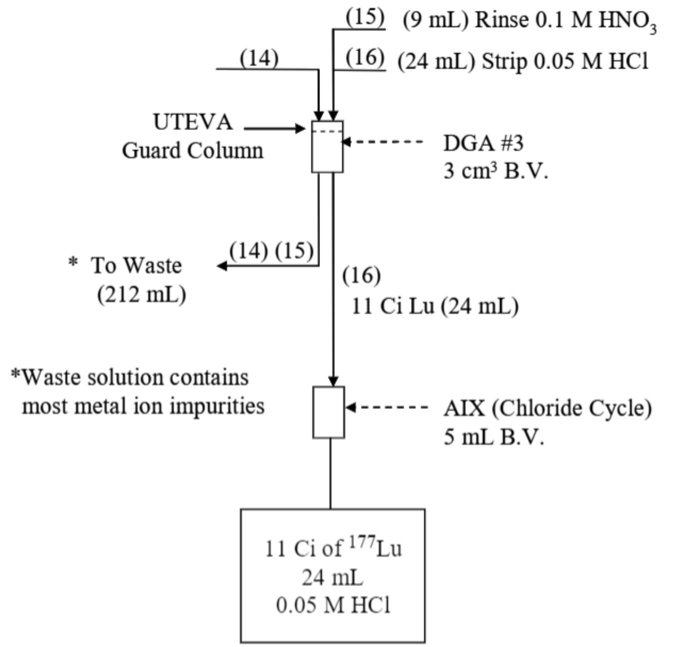


Figure 13. Conceptual flowsheet for the separation of ^{177}Lu from ^{176}Yb: Part C. Secondary Separation System (continued)

Horwitz, E.P. McAlister, D.R. Bond, A.H. Barrans, Jr., R.E. Williamson, J.M. 2005. A Process for the Separation of ^{177}Lu from Neutron Irradiated ^{176}Yb Targets, Applied Radiation and Isotopes, 63, 23-36.

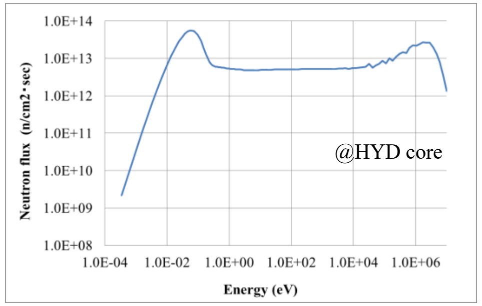
Aim

- In this study, we tracked the behavior of ^{176}Yb and ^{177}Lu through online measurements using a CdZnTe detector to evaluate whether appropriate column separation operations are possible.

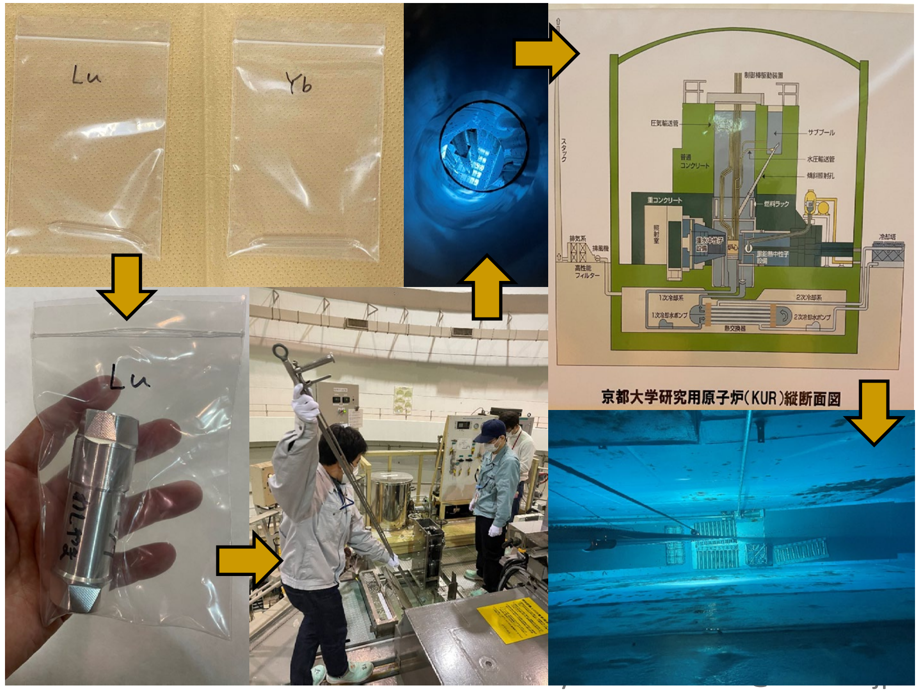
Experimental procedure

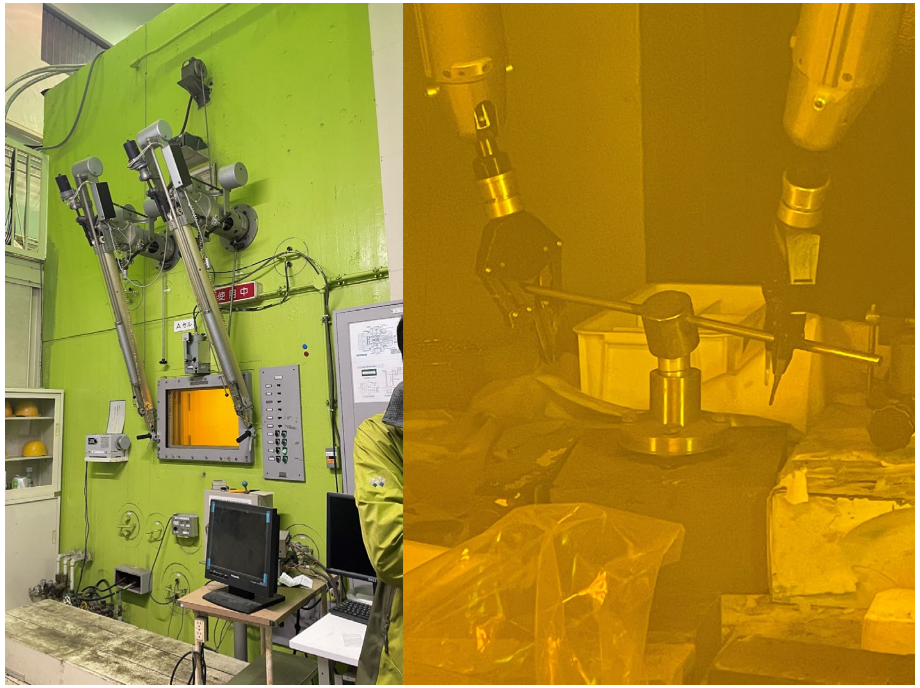
Nuclide	Yb-167	Yb-168	Yb-169	Yb-170	Yb-171	Yb-172	Yb-173	Yb-174	Yb-175	Yb-176	Yb-177
Nat	17.5m	0.123	32.018d	2.982	14.086	21.686	16.103	32.025	4.185d	12.995	1.911h
Enriched	EC, β+	0	EC	0	0.02	0.03	0.03	0.17	β-	**99.75**	β-

- CdZnTe-detector RadAngel (Kromek)
- Enriched $^{176}Yb_2O_3$ Powder (Isoflex) [Enrichment: ^{168}Yb: **0%**, ^{174}Yb: 0.17%, ^{176}Yb: **99.75%]**
- $^{176}Yb_2O_3$ sample (^{176}Yb, 1.0 mg) irradiated for 6 hours at 5 MW thermal neutron flux in the KUR research reactor at Kyoto University's Institute for Advanced Nuclear Science → cooled for 5 days in the pool before opening in a hot cell



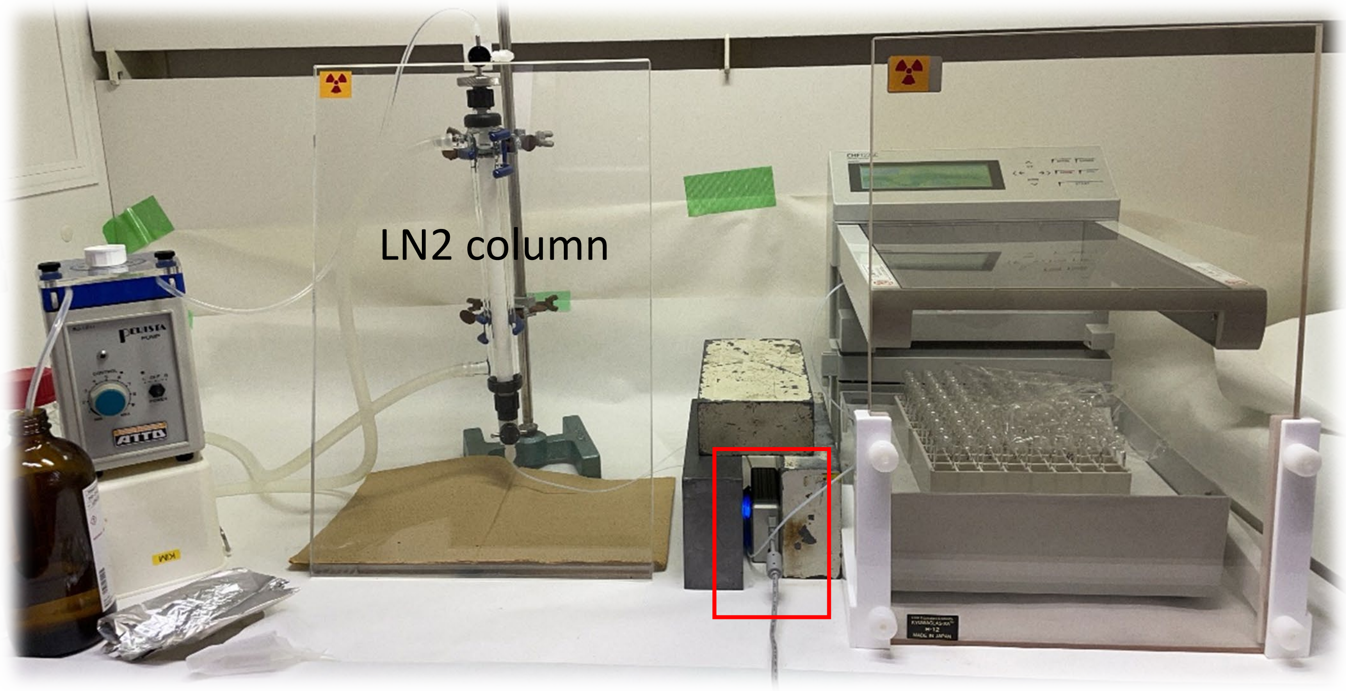
Theoretical calculated Neutron Energy Spectrum (5MW)

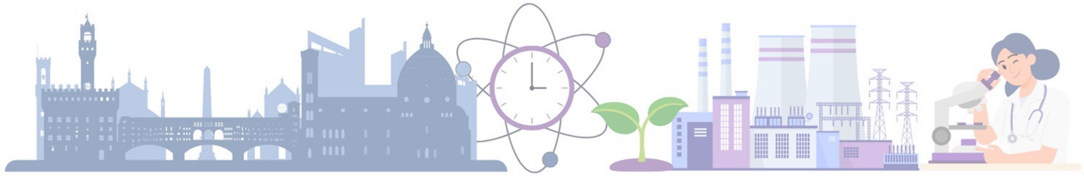




Experimental procedure (cont'd)

- Post-irradiation $^{176}Yb_2O_3$ is dissolved in nitric acid and adjusted to 4 M
- The solution is added to an 11 mmϕ x 240 mm glass column (Kiriya Chemical Co., Ltd.) with a jacket containing extraction chromatography LN2-Resin (Eichrom Co., Ltd.)
- Approximately 500 mL of 1.5 M nitric acid was added to perform the column separation operation
- The solution eluted from the column was collected via a tube into a fraction collector
- The tube was brought into contact with a CdZnTe detector for online measurement
- Collected 250 drops of eluate per fraction into over 50 test tubes
- Used a Ge detector (ORTEC) to confirm eluted fractions
- Compared with the elution curve obtained from CdZnTe detector monitoring





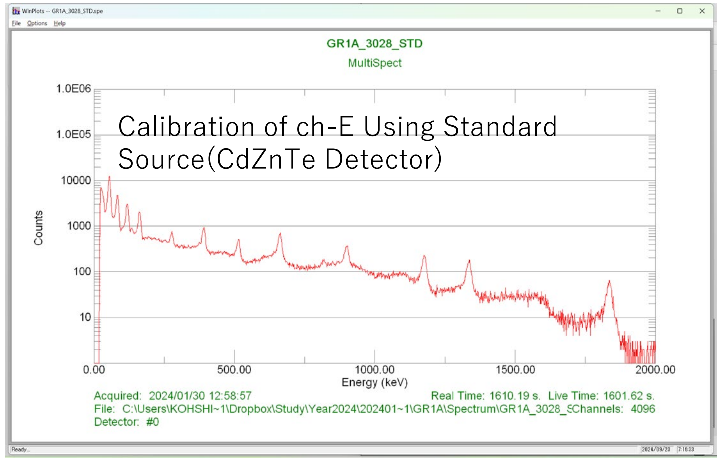
CdZnTe and collection setup

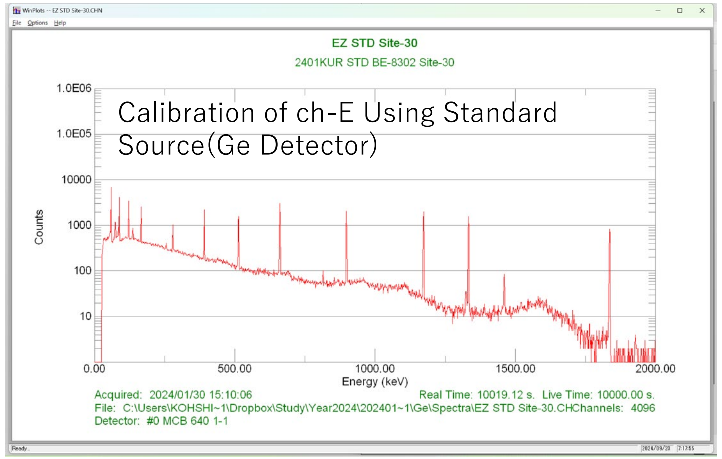
- ROI settings for CdZnTe detector: After calibrating energy and channels using a standard source, confirmed at the photoconductive peaks of 396.3 keV (13.2%) for ^{175}Yb and 208 keV (10.4%) for ^{177}Lu by irradiating with natural isotope compositions of Yb and Lu, respectively
- γ-ray spectra with CdZnTe detectors were automatically collected using MultiSpectAnalyser software (Kromek).
- Simultaneously collectible trend graphs output count rates every 15 seconds based on ROI area.

- γ-ray spectrum measurements with Ge detectors were performed for 5 minutes per fraction.
- Samples with high count rates were measured at a maximum distance of 30 cm on Ge detector. Count rates are displayed as net counts.
- Using the count efficiency determined with the standard source, the radioactivity at the end of irradiation and during handling was calculated.

CdZnTe-detector, RadAngel (Kromek)

- 5x5x5mm CdZnTe crystal
- 4K MCA installedcompact size
- USB-powered
- Suitable for online remote measurement under high radiation exposure
- 237,000 JPY (w/o tax) @Y2019
= 2,000 EUR (1 EUR = 117 JPY)



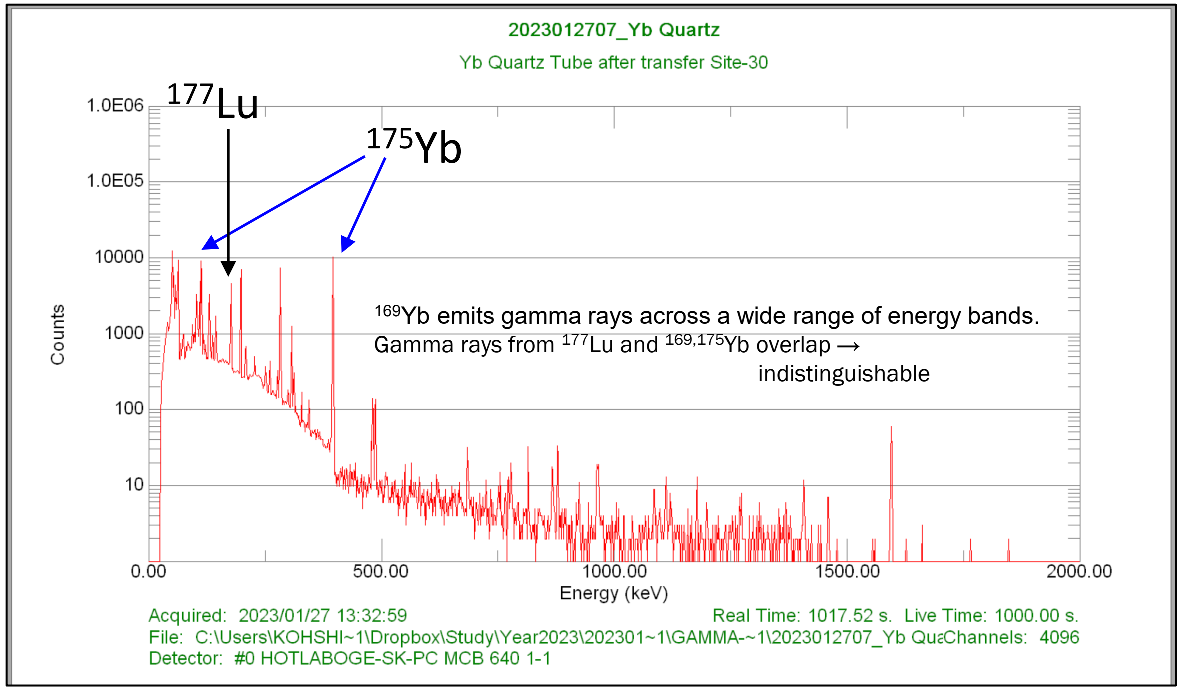


Gamma-ray spectra of irradiated Yb_2O_3

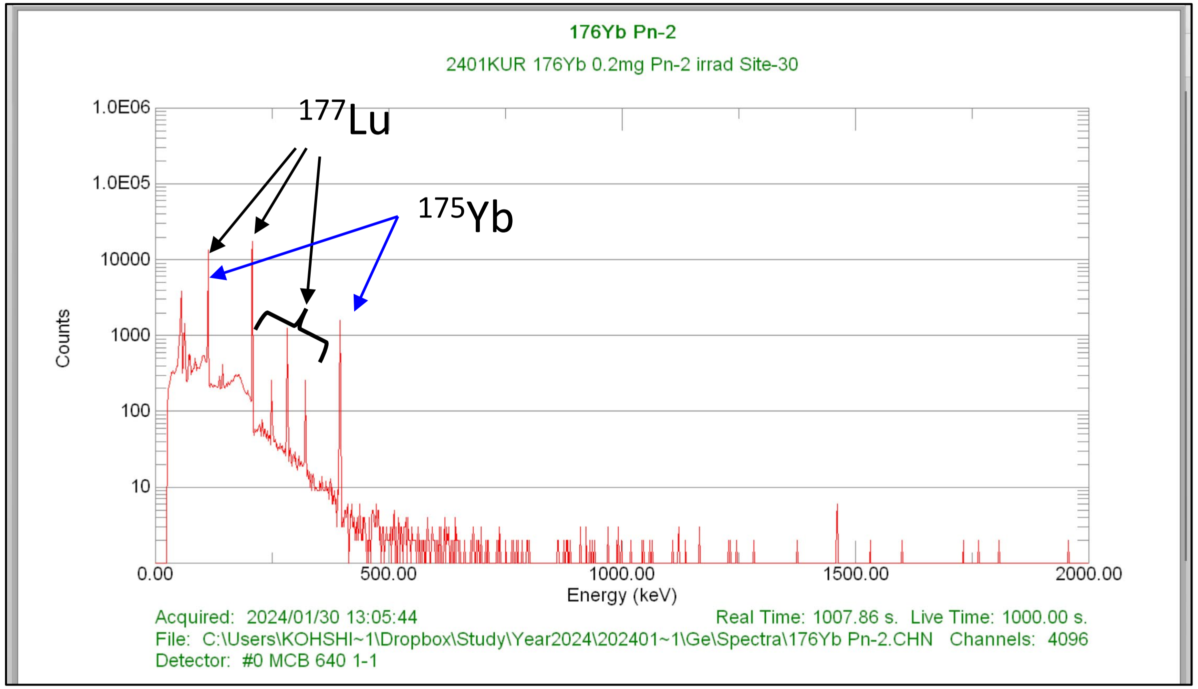
Gamma-ray energyand emission rate (%)

Yb-169 (32.018d)		Yb-175 (4.185d)		Lu-177 (6.6443d)	
Energy [keV]	Intensity [%]	Energy [keV]	Intensity [%]	Energy [keV]	Intensity [%]
307.7	10.1	396.3	13.2	321.3	0.2
307.5	0.5	282.5	6.1	249.7	0.2
261.1	1.7	251.5	0.2	208.4	10.4
198.0	35.9	144.9	0.7	112.9	6.2
177.2	22.3	137.7	0.2	71.6	0.2
130.5	11.4	113.8	3.9		
129.9	0.5				
118.2	1.9				
109.8	17.4				
93.6	2.6				
63.1	43.6				
63.0	2.2				
50.9	0.5				
50.6	0.5				

An Irradiated ^{nat}Yb sample (Ge-detector measurement)



An Irradiated ^{176}Yb sample (Ge-detector measurement)



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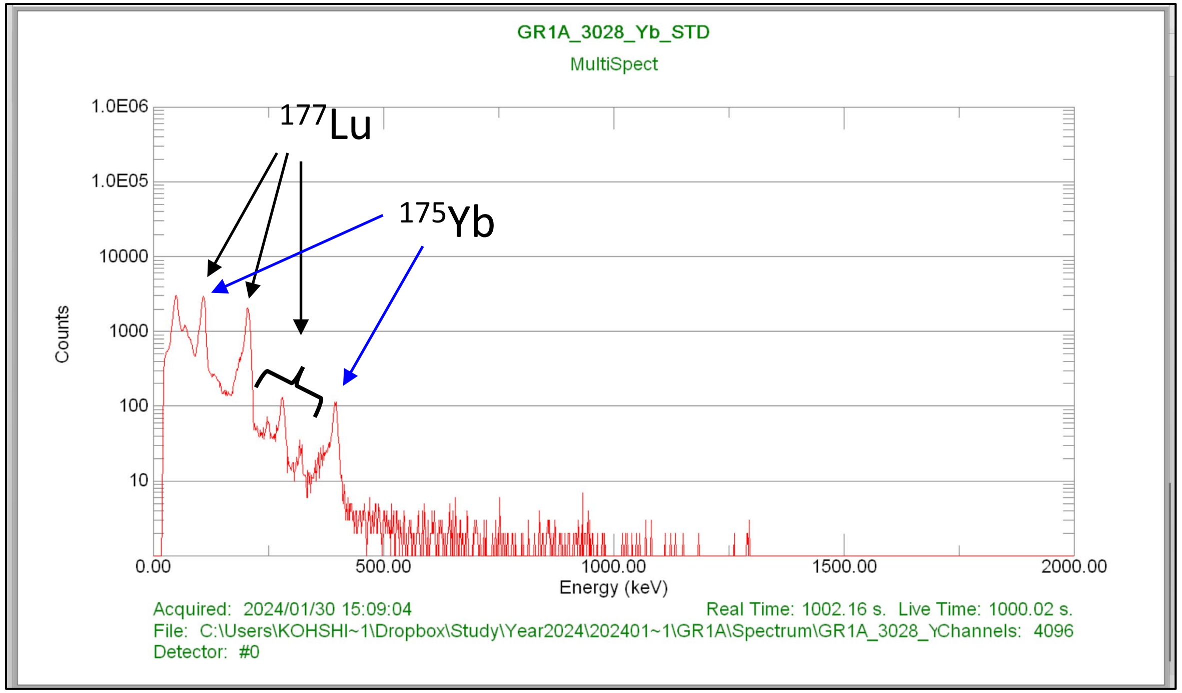
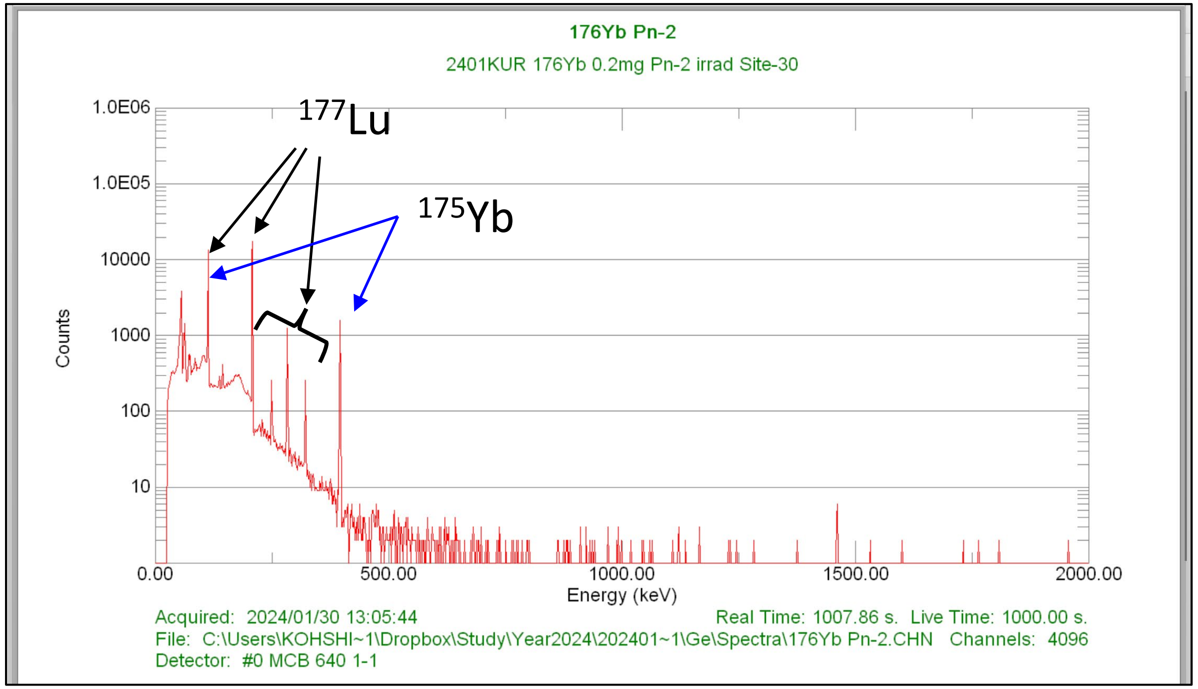
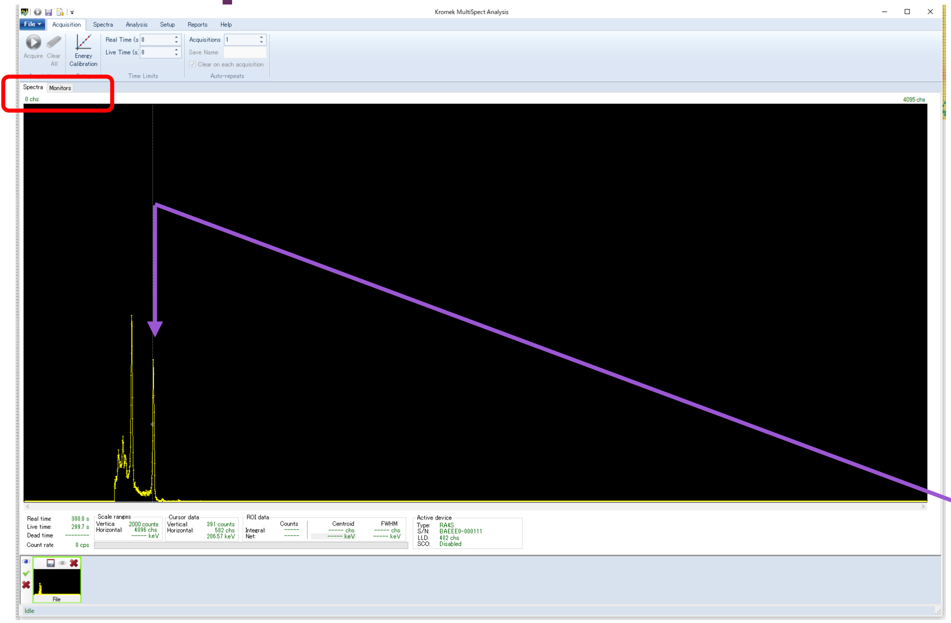
An Irradiated ^{176}Yb sample (**CdZnTe**-detector measurement)

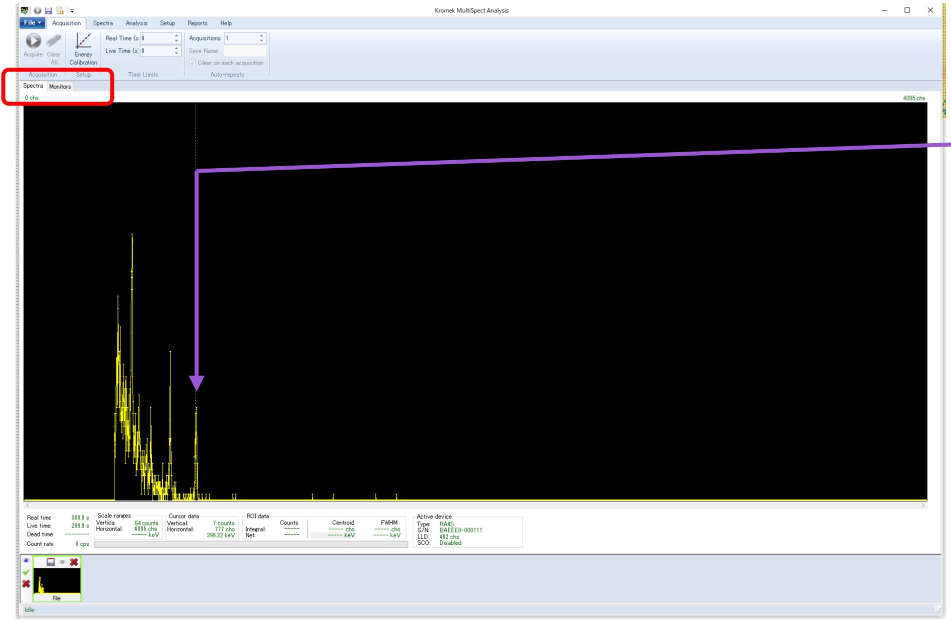


An Irradiated ^{176}Yb sample (**Ge**-detector measurement)



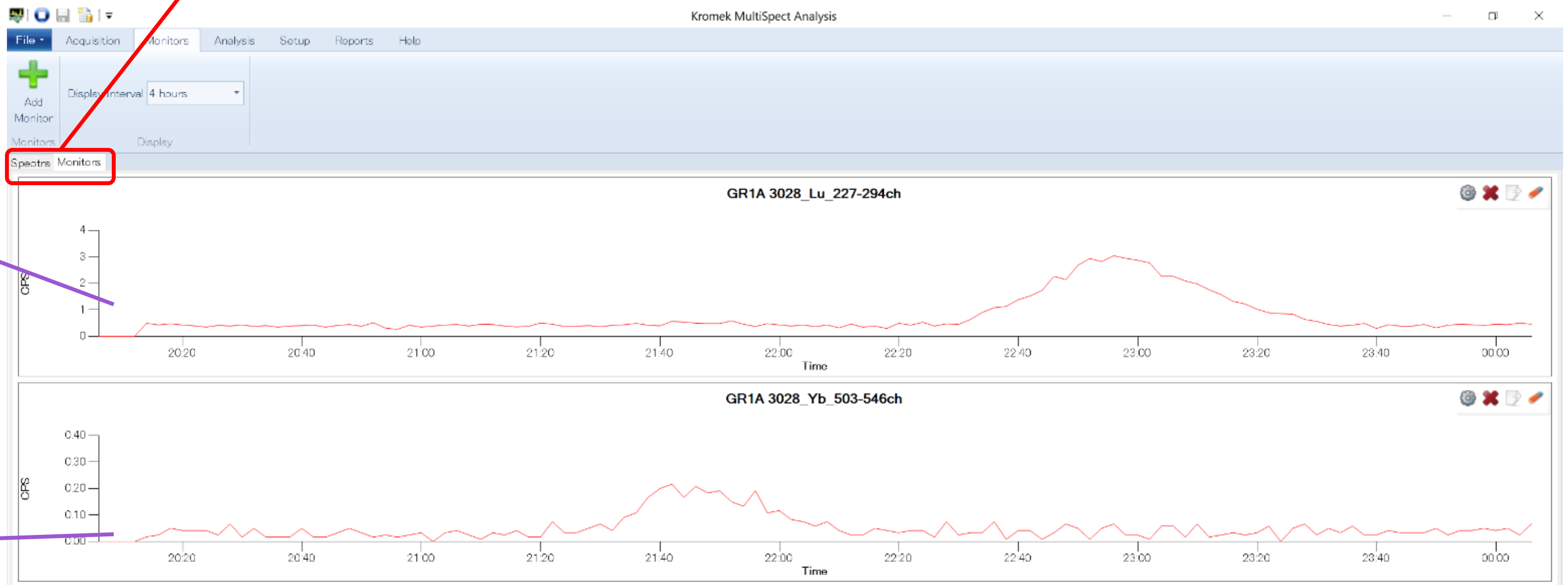
Output data from CdZnTe detectors





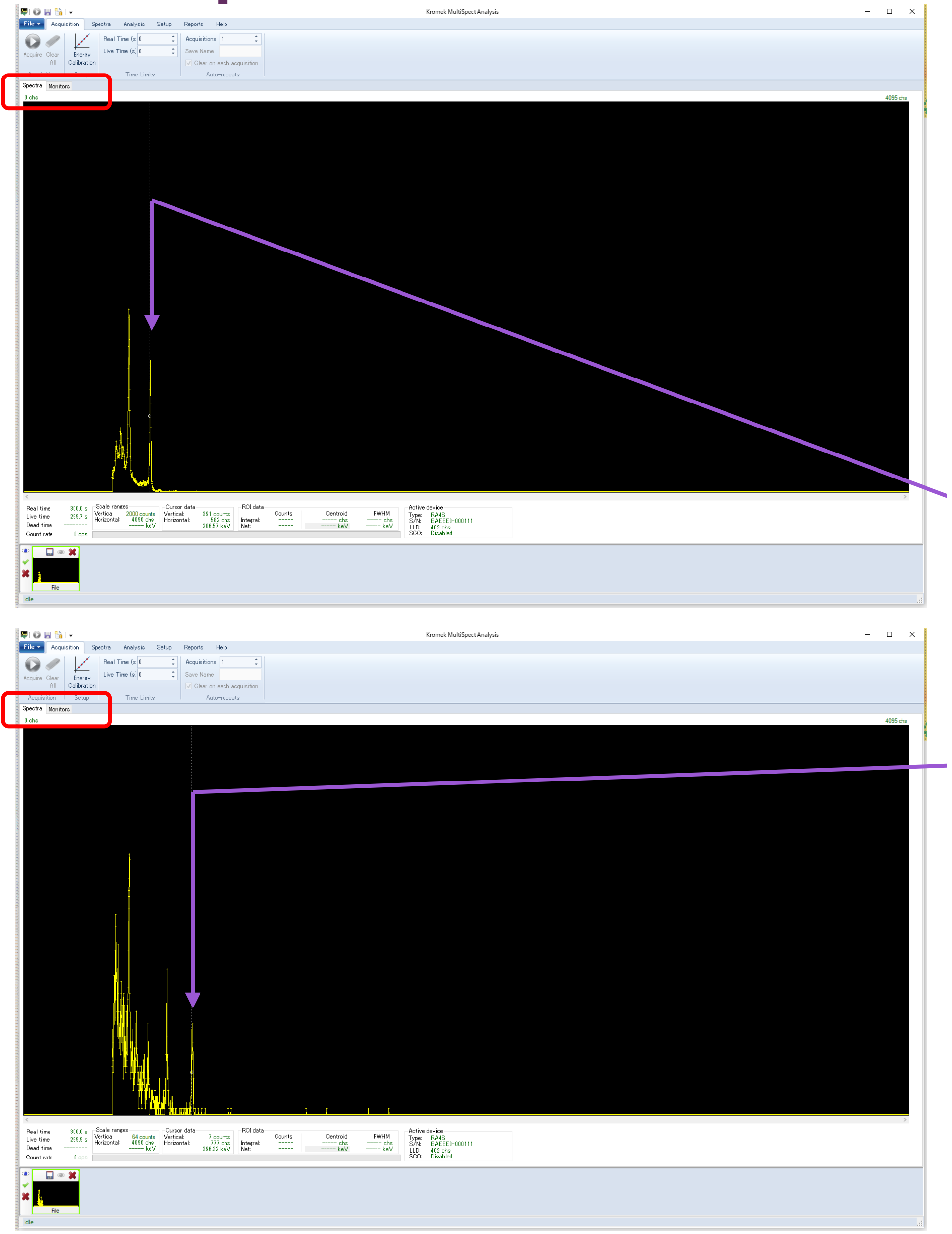
The control software for the CdZnTe detector allows users to switch between windows to alternately view the gamma-ray spectrum and trend.

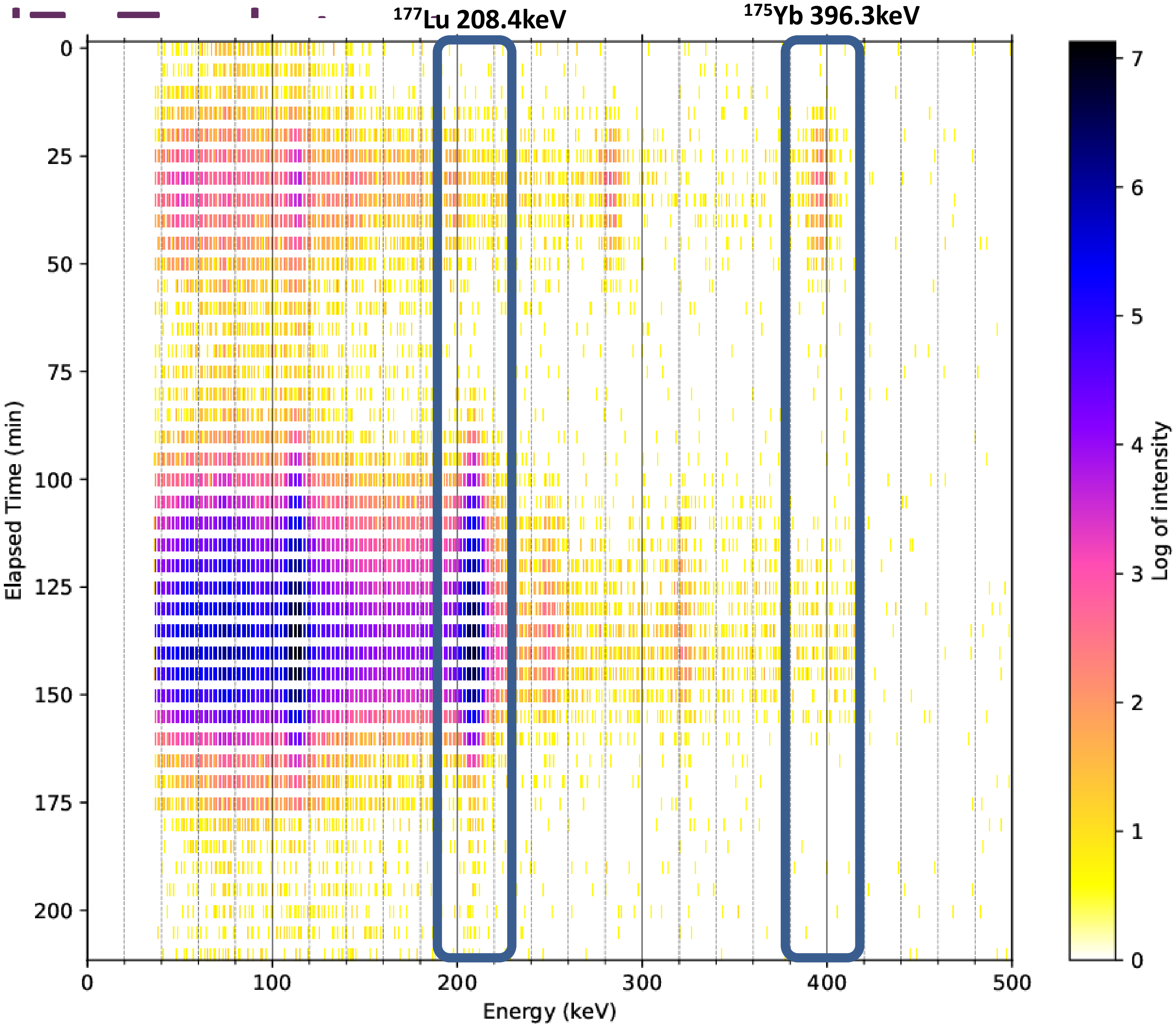
Trend display for 2-minute interval collection



The elution curves of ^{175}Yb (incl. ^{176}Yb target) and ^{177}Lu in column separation can be accurately determined.

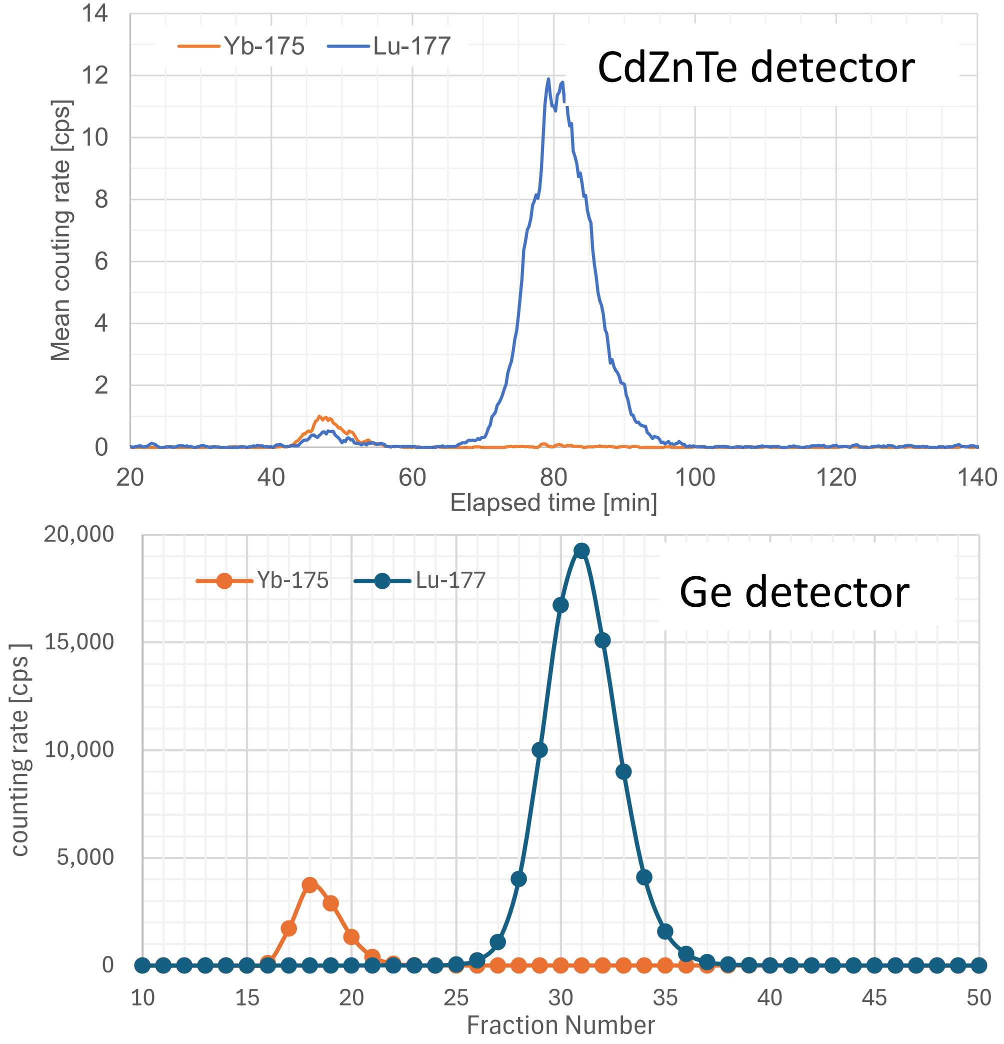
Output data from C

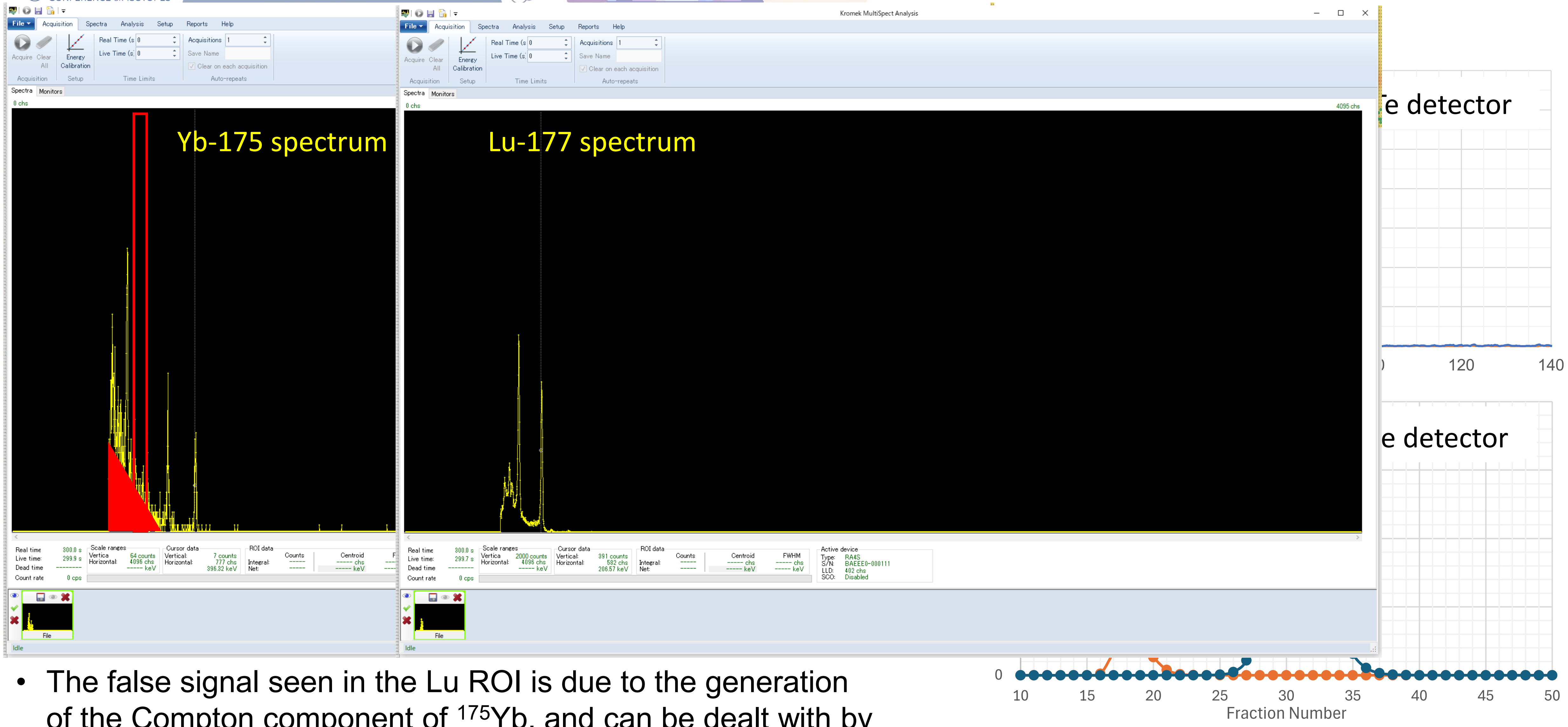




Comparison with Ge-detector

- Qualitative analysis using Ge detectors: Confirmed the formation of highly radioactive ^{177}Lu and low-radioactive ^{175}Yb ($T_{1/2}$=4.19 days) in samples 5 days after irradiation
- By using an enriched ^{176}Yb, the formation of interfering nuclide ^{169}Yb could be avoided
- Regarding the separation of ^{177}Lu and ^{176}Yb: The presence of spike ^{175}Yb tracer is necessary to confirm that ^{177}Lu is reliably separated from the target
- ^{175}Yb (radioactive) was produced due to the presence of ^{174}Yb (stable) at 0.17% in the ^{176}Yb enriched isotope
- ^{175}Yb emits higher-energy γ rays than ^{177}Lu, and it elutes earlier than ^{177}Lu in column separation → Less impact during monitoring of the Lu fraction
- The elution curves for ^{175}Yb and ^{177}Lu obtained with CdZnTe and Ge detectors showed the same trend.
- The false signal seen in the Lu ROI is due to the generation of the Compton component of ^{175}Yb, and can be dealt with by software processing.





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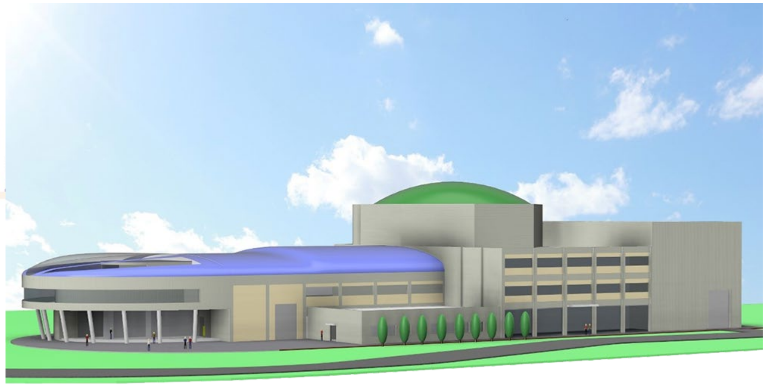
Conclusion

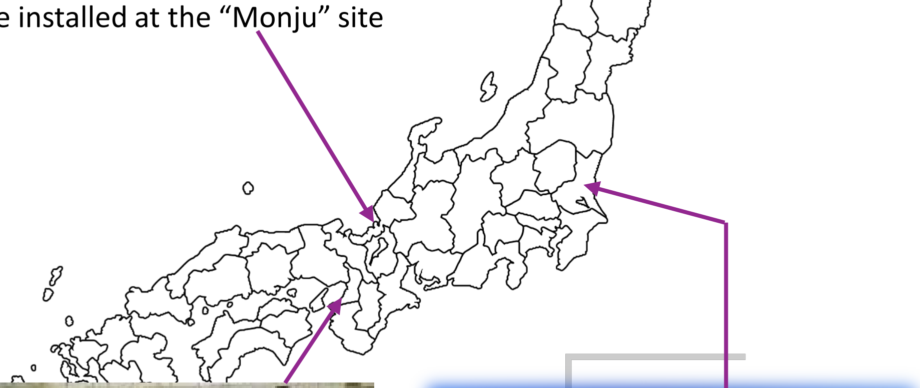
- This study used a CZT detector for online γ monitoring during column separation of enriched ^{176}Yb and ^{177}Lu.

- The enriched isotope enabled clear distinction between high-activity low-energy γ-rays of ^{177}Lu and low-activity high-energy γ-rays of ^{175}Yb.

- This approach supports precise ^{177}Lu fraction recovery and reduces worker exposure during high-activity separations in hot cells.



New research reactor to be installed at the “Monju” site



Kyoto University Research Reactor

Japan Atomic Energy Agency JRR-3

As KUR will cease operation and be decommissioned in June 2026, this technology and knowledge will be applied to JAEA's 20 MW reactor JRR-3 going forward, and ultimately deployed to the new research reactor planned for construction in Tsuruga, Fukui.

Acknowledgement

This research was conducted as a project study under the National Joint Research Program at the Institute for Advanced Nuclear Science and Engineering, Kyoto University. We extend our deepest gratitude to Mr. Ryo Okumura, Mr. Yasushi Yoshino, and Mr. Naoki Yoshinaga for their support during the joint research.