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Annual Users' Conference

ADVANCING RADIATION SAFETY. EMPOWERING PROGRESS.

M Resort, Henderson, NV | June 15 – June 18

MIRION TECHNOLOGIES

Advancing Radiation Safety.
Empowering Progress.

A Defensible Framework for Radionuclidic Purity and Quantification
Gamma Spectroscopy, Uncertainty, and Improving Time to Product Verification

Henrik Persson

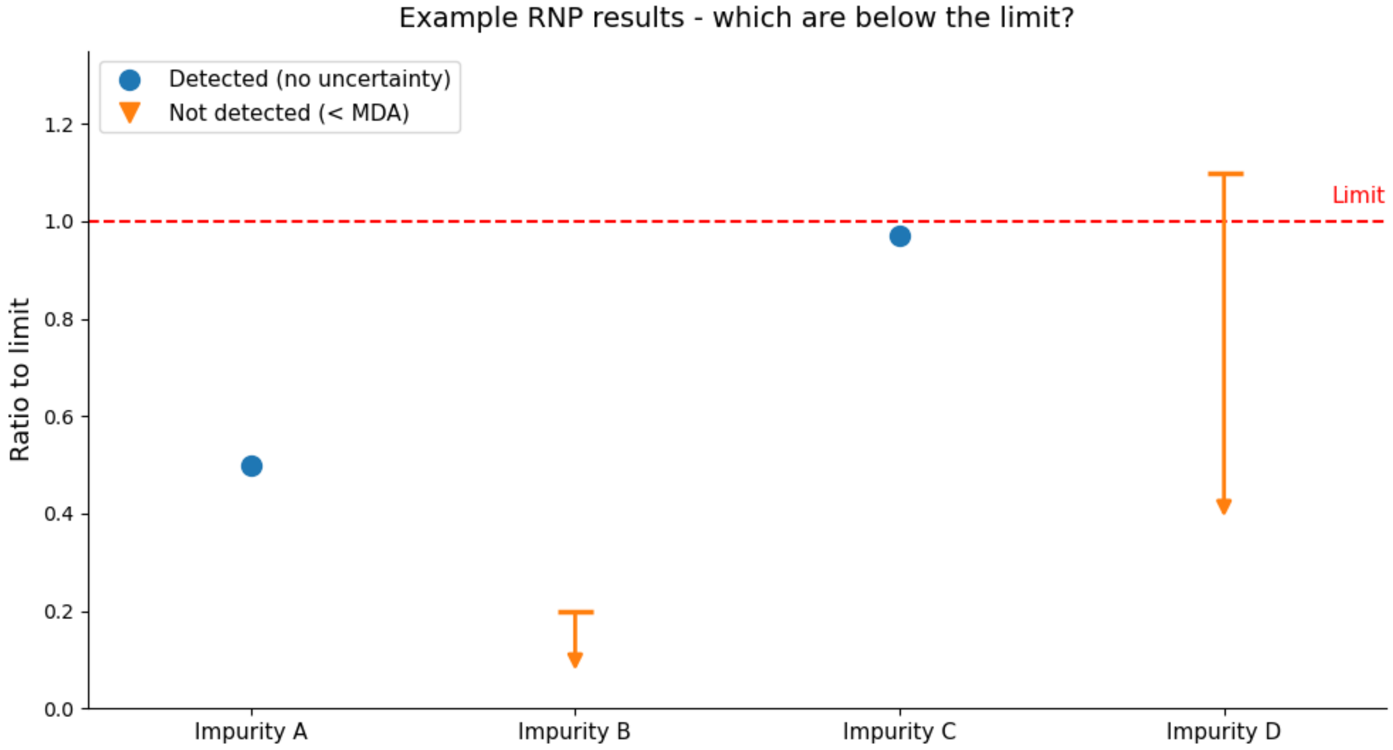
Principal Research Scientist

Mirion Connect | Annual Users' Conference 2026

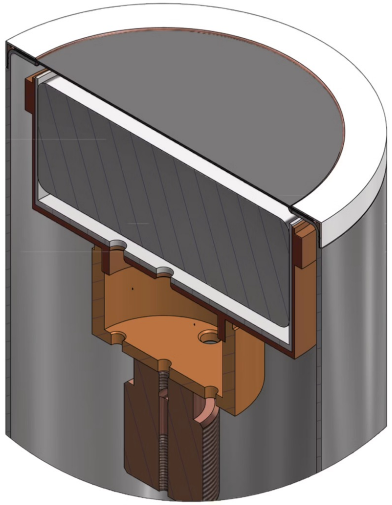
Henderson, NV

Introduction

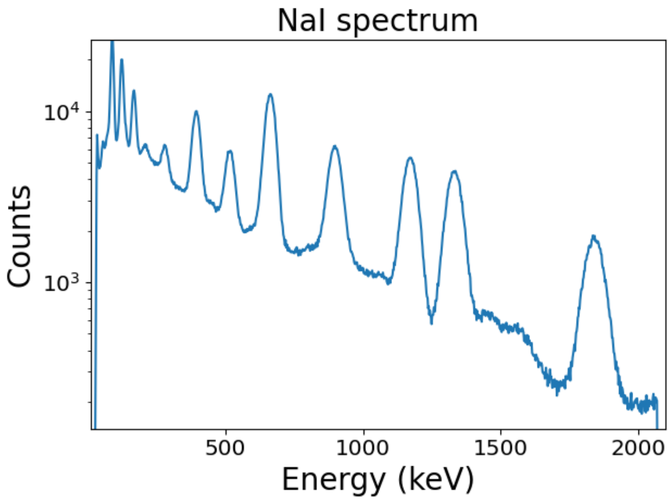
- *Need for a way to calculate RNP within Mirion's software*
- *What's the state-of-the art and can we improve it?*
- *Need for a physically interpretable quantity*

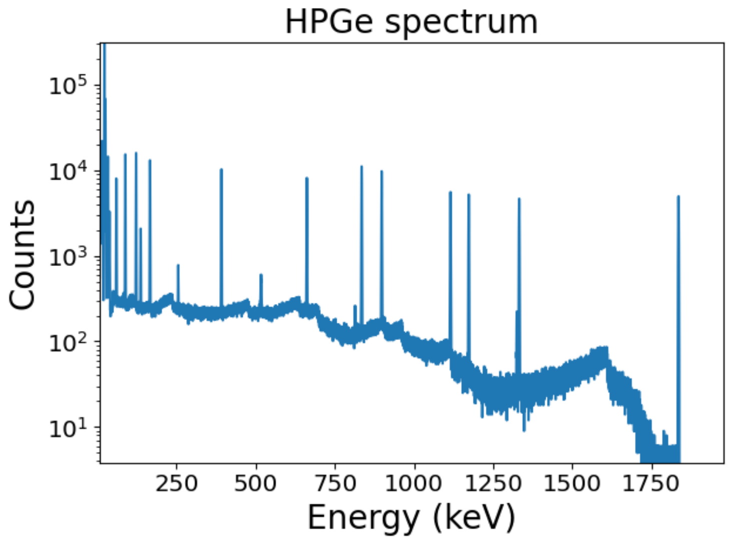


Detector and software fit for purpose



Activity





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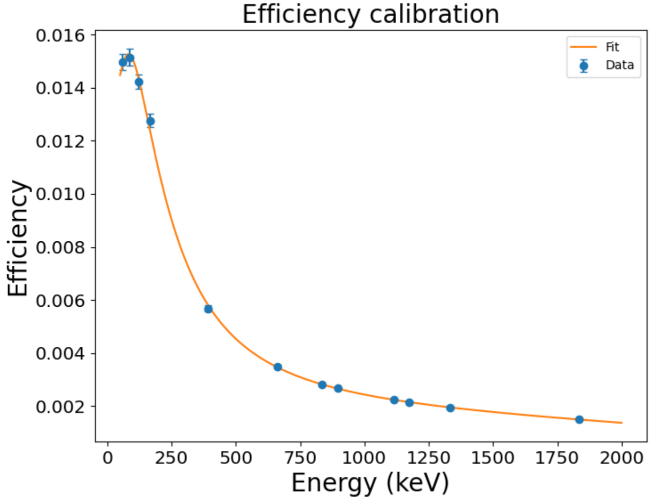
Making quality measurements in gamma spectrometry

"A MEASUREMENT WITHOUT UNCERTAINTY IS NOTHING"

- *Efficiency calibration ~ 1.5 – 2%*
- *Peak Area calculation ~ 0.5 – 60%*
- *Radionuclide decay data ~0.5 – 30%*
- *Activity calculation and interference correction*
- *Total uncertainty about ≥ 2%*



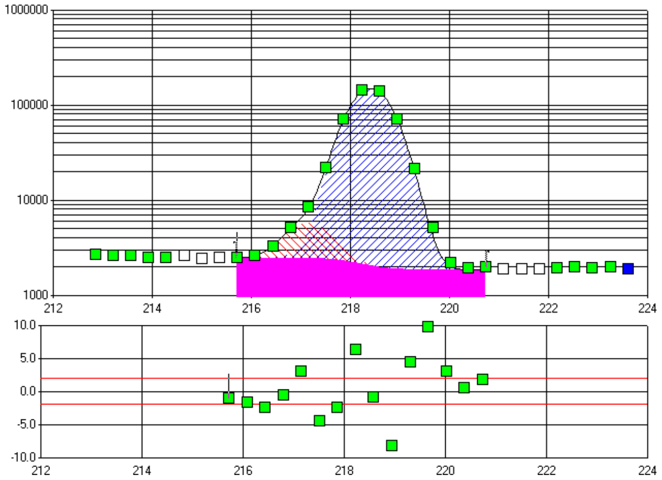
^{177}Lu - Decay data

Data | Emissions | Tools | Radioactive chain | Scheme

Emissions

Emissions (11 lines) sorted by increasing energy

Energy (keV)	Intensity (%)	Type	Origin*	Levels Start*	Levels End*
8.9268 (-)	3.12 (6)	X_L	Hf		
54.612 (-)	1.555 (27)	$X_{K\alpha 2}$	Hf		
55.7909 (-)	2.72 (5)	$X_{K\alpha 1}$	Hf		
63.292 (-)	0.898 (21)	$X_{K'\beta 1}$	Hf		
65.1427 (-)	0.240 (7)	$X_{K'\beta 2}$	Hf		
71.6425 (6)	0.1716 (14)	γ	Hf-177	3	2
112.95005 (36)	6.223 (32)	γ	Hf-177	1	0
136.7245 (5)	0.04731 (44)	γ	Hf-177	2	1
208.3661 (2)	10.425 (35)	γ	Hf-177	3	1
249.6742 (6)	0.2007 (12)	γ	Hf-177	2	0
321.3159 (6)	0.2096 (14)	γ	Hf-177	3	0



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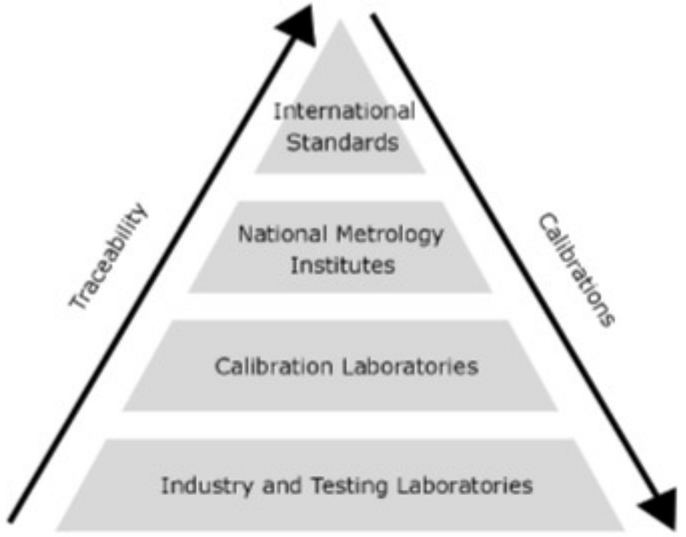
Traceability

"ONE CAN DO NON-TRACEABLE MEASUREMENTS AND BE RIGHT; ONE CAN DO TRACEABLE MEASUREMENTS AND BE WRONG"

- *Unbroken chain of measurements back to the SI unit*
- *Direct comparison of radionuclide with traceable activity*
  - *Dose calibrator*
  - *Gamma spec calibration with same radionuclide*
- *Efficiency calibration using a fitted function with approved radionuclide decay data.*
  - *Gamma spec for a different radionuclide than used for calibration*



Radionuclidic Purity Measurements

Objective

Determine if the activities of a set of radionuclide impurities are below a percent limit of the primary radionuclide activity. **This activity ratio is called the Radionuclidic Purity**.

Measurement

For impurity radionuclides: Gamma spectrometry (or potentially Alpha Spec, Mass Spec, or LCS)

For primary radionuclides: Gamma spectrometry or other

Easy, right?

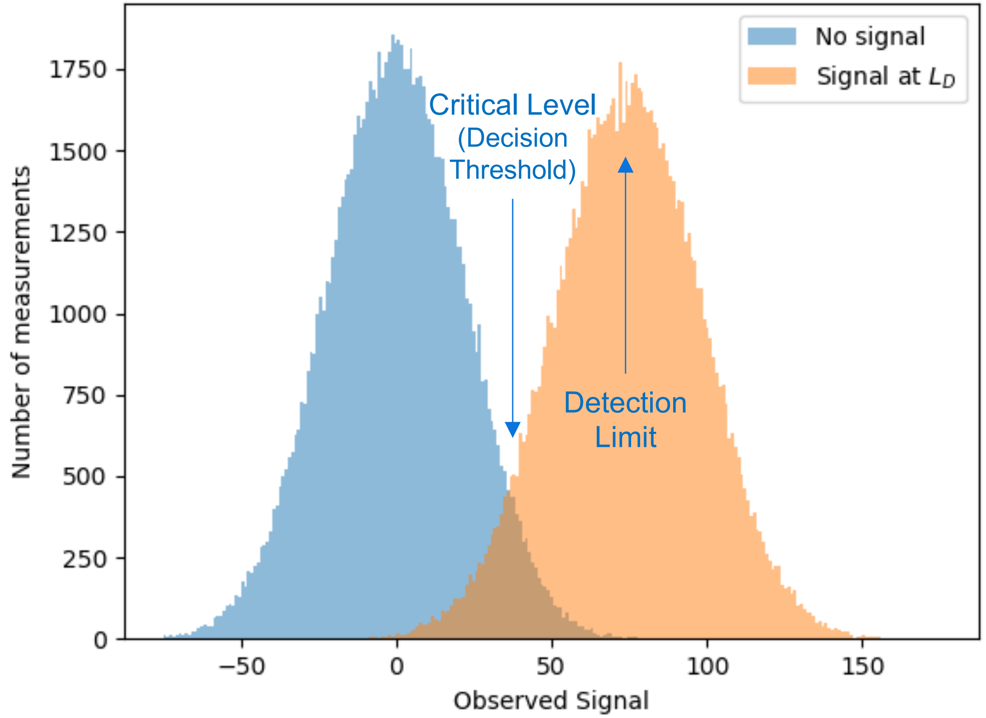
Just divide the activities, but what about the uncertainties?

Activity measurements have uncertainty – so how certain is our Radionuclidic Purity calculation?

And what to do when the impurity isn't detected?

What's the right question that we want to answer

- *Currie and ISO11929 Minimum Detectable Activity approach answers the questions:*
  - *Is the measured signal large enough that we are 95% sure that it is not consistent with 0? (Critical level or decision threshold)*
  - *Given a background measurement, how large does the activity need to be that we get a signal above the critical level 95% of the time?*
- *For Radionuclidic purity measurements it is a different question:*
  - *Is the signal small enough that we are 95% sure that it is below the percent limit?*



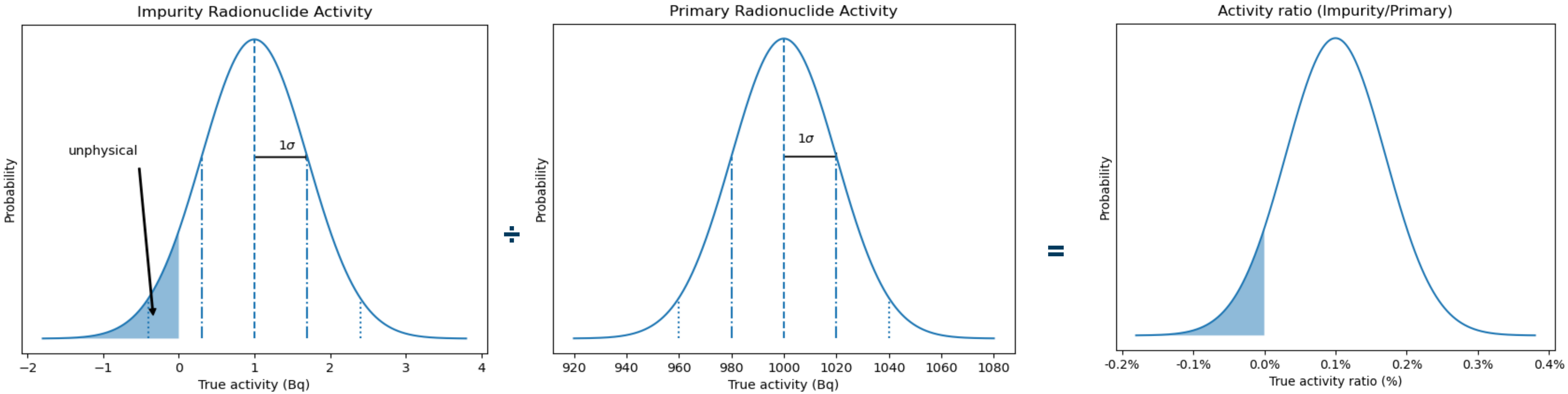
A New Algorithm: Determining a ratio including uncertainties

Consider a measurement of an impurity radionuclide and a primary radionuclide, each with an activity and activity uncertainty:

- *The uncertainties of the activity measurements are normally distributed*
- *The measured value is the most likely value*
- *68% probability that the true value is within the +/-1σ uncertainty of the measured value*

Since the true value for the activities is not known, the true value of the impurity-to-primary activity ratio is not known either.

That said, it is known that the true radionuclide activity cannot be negative - although one may measure a negative activity.



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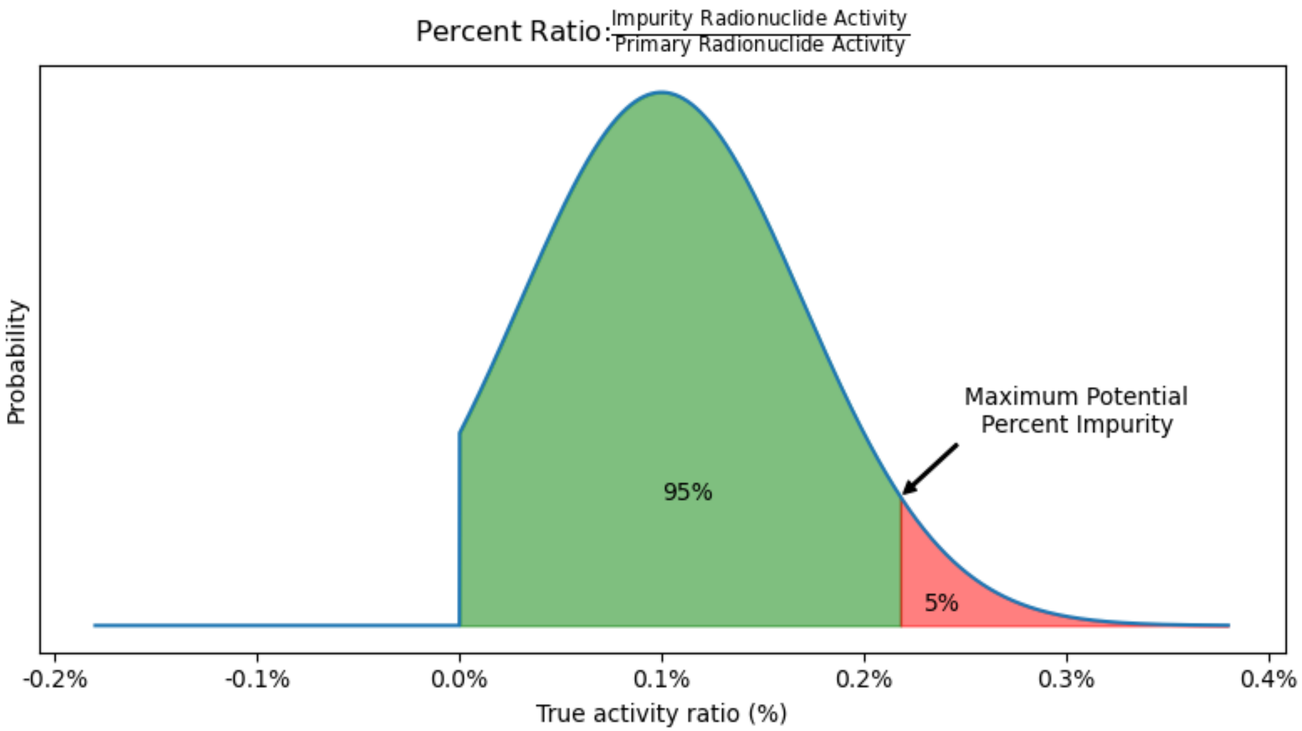
A New Algorithm: Determining a ratio including uncertainties

The probability distribution of ratio of the two activity measurements provides a range of potential values for the true impurity ratio:

- *The most likely value of the true impurity ratio is the calculated ratio of the measured activity values*
- *The possible true values of the ratio follows the probability distribution, which can be greater than the calculated ratio*



Introducing the Maximum Potential Percent Impurity (MPPI) Value

- *An impurity ratio value that is greater than the true activity ratio with 95%* confidence*

  ** This is the 1 – α confidence, which can be specified*
- *If the MPPI is less than or equal to a maximum impurity percentage, one can conclude that the impurity activity is less than this limit with at least 95% confidence.*

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Report results

- *ACCEPTABLE RESULTS*

10/4/2024 4:22:44PM Page 2 of 2

Analysis Report for Sample ID 12345
QA Measurement of Lu-177 Production

Radionuclide Impurity Report

MPPI Activity Reference: Activity of Primary Radionuclide only
Alpha Confidence: 5.000 %
Nuclide Library: LU177_INDIRECT.NLB

Reference Date: 10/4/2024 4:16:03PM

Radionuclide	*Impurity Analysis Category*	*Activity (kBq/units)*	*Activity Uncertainty at 1.0 sigma*	*MDA / Reference Activity*	*Maximum Potential Percent Impurity*	*Percent Impurity Limit*
Lu-177	Primary	4.547E+02	2.14E+00%	-------	------	------
Yb-169	Impurity	---------	---------	0.012%	0.005%	0.010%
Yb-175	Impurity	---------	---------	0.002%	0.001%	0.100%
Sum of Impurities :					0.006%	0.100%

>> Sample analysis results are below the specified radionuclide impurity limits at reference time 10/4/2024 4:16:03PM.

>> Minimum Radionuclidic Purity : 99.994%

The maximum potential percent impurity (MPPI) is the greatest relative percent activity of the impurity compared to the activity reference at the alpha confidence for this measurement, taking into account their respective uncertainties. There is a 95.00% probability that the true impurity percent is at or below the MPPI.

- *HIGH IMPURITY RESULT*

10/4/2024 4:35:42PM Page 2 of 2

Analysis Report for Sample ID 12346
Impurity analysis at acquistion time and two weeks later

Radionuclide Impurity Report

MPPI Activity Reference: Activity of Primary Radionuclide only
Alpha Confidence: 5.000 %
Nuclide Library: LU177_INDIRECT.NLB

Reference Date: 10/18/2024 4:28:07PM

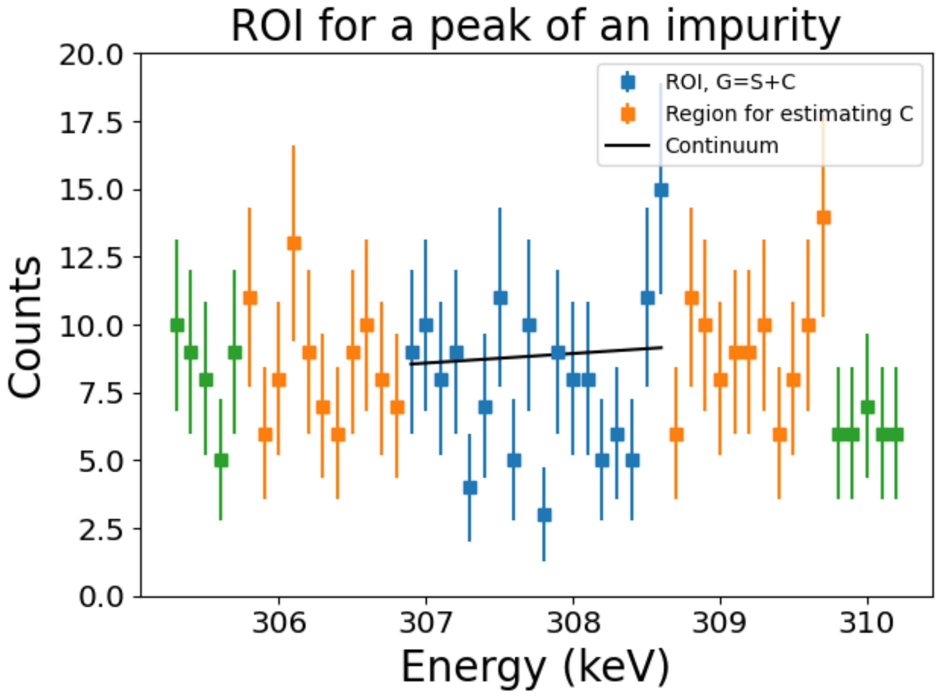
Radionuclide	*Impurity Analysis Category*	*Activity (kBq/units)*	*Activity Uncertainty at 1.0 sigma*	*MDA / Reference Activity*	*Maximum Potential Percent Impurity*	*Percent Impurity Limit*
Lu-177	Primary	1.055E+02	2.14E+00%	-------	------	------
Yb-169	Impurity	---------	---------	0.037%	0.016%	0.010%
Yb-175	Impurity	---------	---------	8.86E-04%	4.60E-04%	0.100%
Sum of Impurities :					0.017%	0.100%

>> Minimum Radionuclidic Purity : 99.983%

The maximum potential percent impurity (MPPI) is the greatest relative percent activity of the impurity compared to the activity reference at the alpha confidence for this measurement, taking into account their respective uncertainties. There is a 95.00% probability that the true impurity percent is at or below the MPPI.

Determining Radionuclidic Impurity Ratio When Impurity Activity is Not Detected

- *Apex-Gamma can always calculate an activity and an MDA even when the radionuclide has not been detected.*
- *Can the MDA be used to report an Impurity Ratio?*
  - *An activity at the value of the MDA will have a 95% probability to result in a detectable signal*
  - *The MDA is conservative when the impurity is not present*
  - *If the impurity activity is detected in the measurement, then the MDA cannot be used.*
- *The MPPI algorithm can be used for both detected impurity activity and not detected activity.*



Peak Area (counts)	Unc (counts)	L_C (counts)	L_D (counts)
-16.75	16.56	28.1	58.7

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That’s great!
but does it work?

Let's try it on measurements

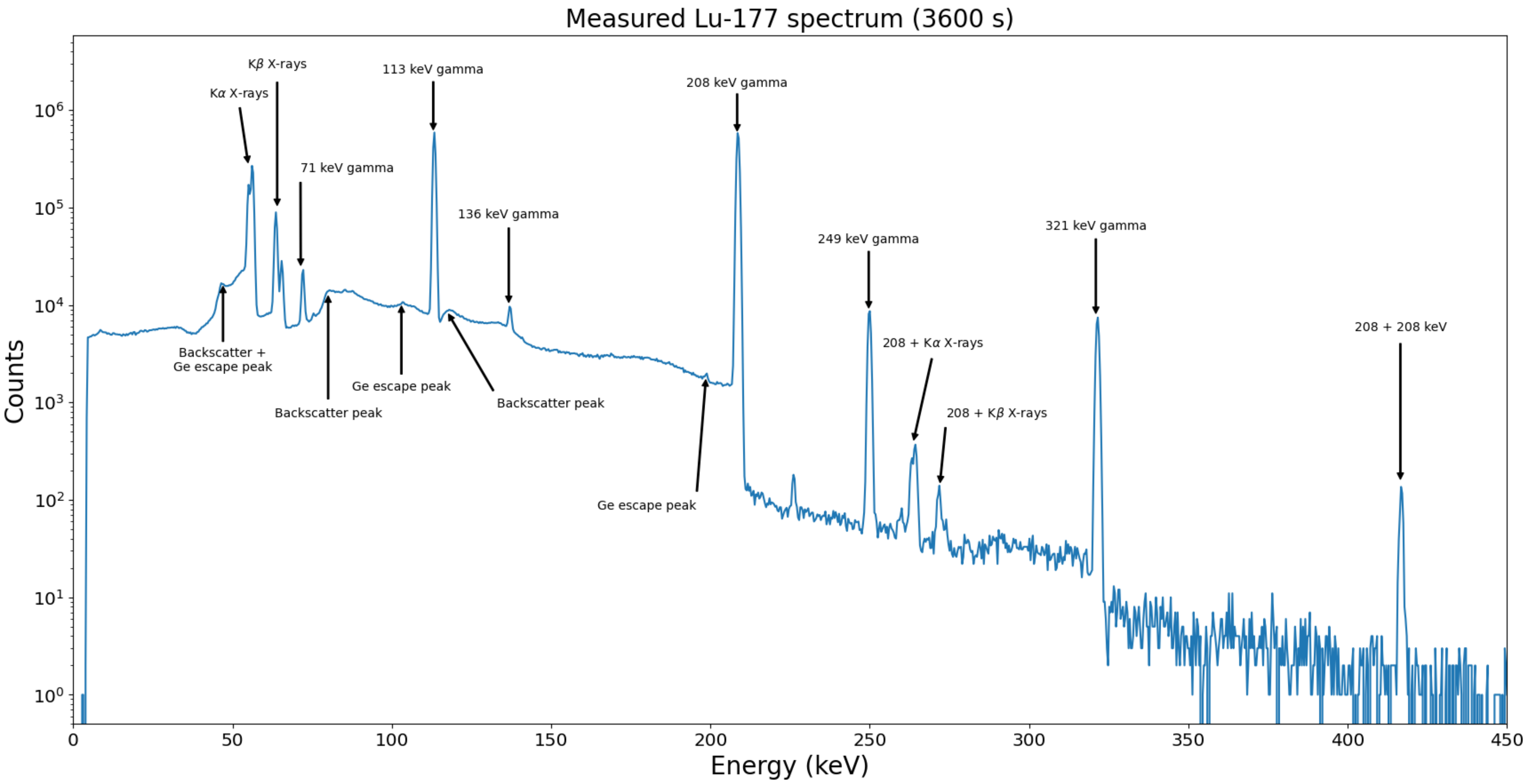
Measurements and photos provided by Elys Jamieson of BC Cancer

Measurement protocol

- *10 second measurement*
  - *Stop, save then restart*
- *Total measurement time 1 hour*
- *Analyze every measurement*
- *Gives the measurement time evolution of analysis results and possibility to compare time for a quantity to reach a limit or a specific uncertainty.*
- *Efficiency calibration using a traceable source with same geometry as measurements*
- *Measured three radionuclides*
  - *Lu-177*
  - *Ac-225*

Lu-177

- *Half-life: 6.6443 days*
- *β^- decay*
- *Main gamma emissions: 113, 208, 321*
- *Possible impurities*
  - *Lu-177m 0.07% (direct production)*
  - *Yb-169 0.01%, Yb-175 0.1% (indirect production)*
  - *Yb-169 most challengin[g] – lower emission energies*



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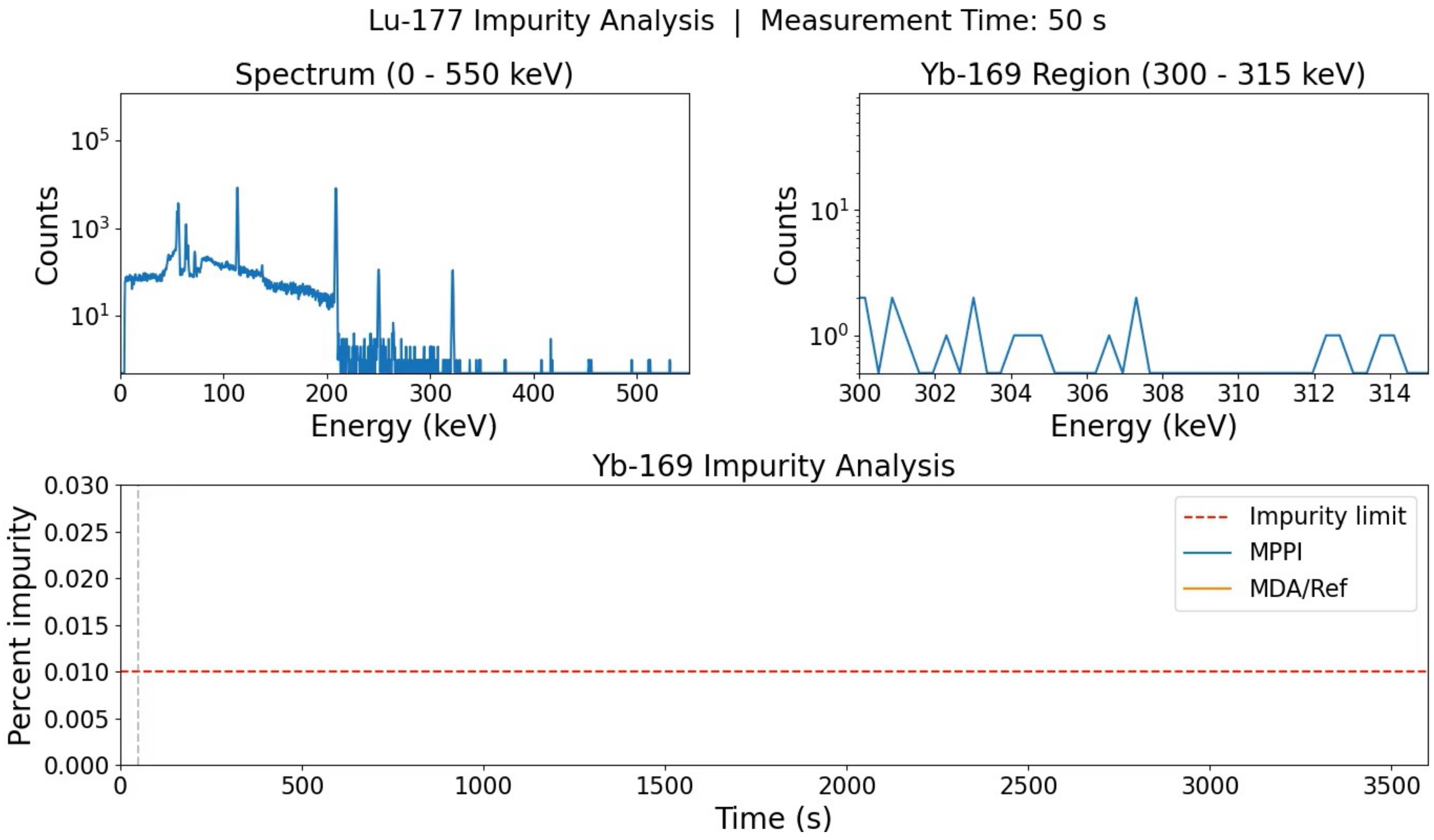
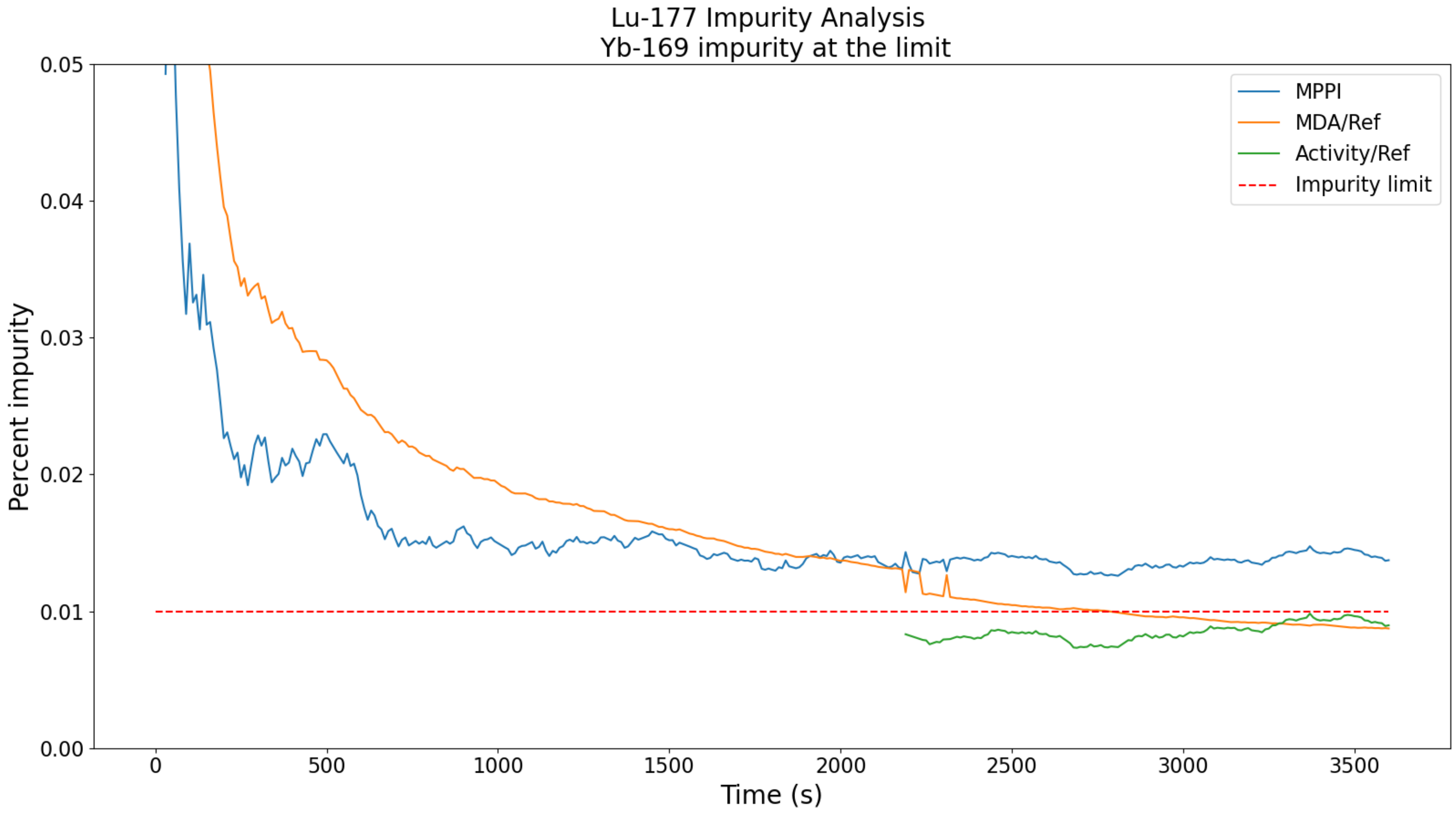
Yb-169 impurity – Time evolution



MPPI - With an impurity present

- *No impurity present in measurement.*
- *Injected a peak at 307 keV with the count rate of Yb-169 impurity at the limit.*
- *MPPI works for both cases*



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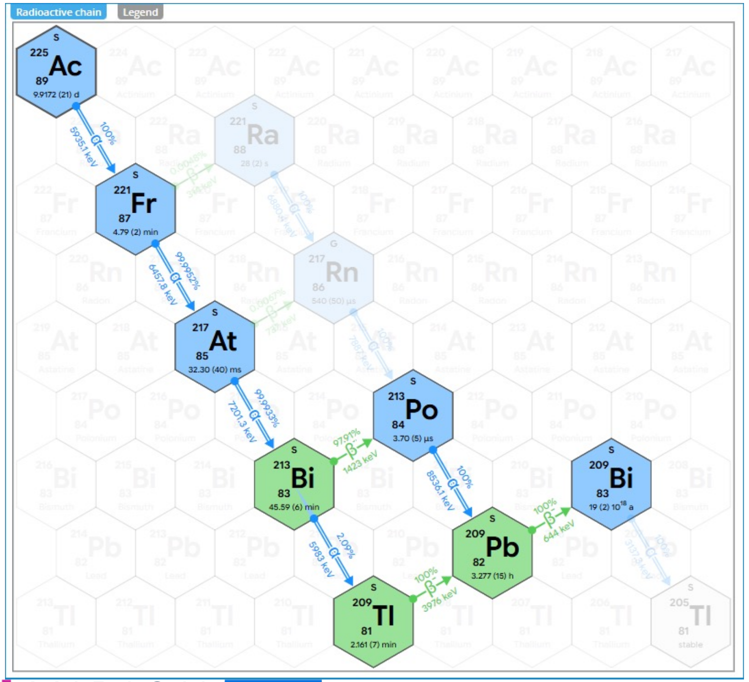
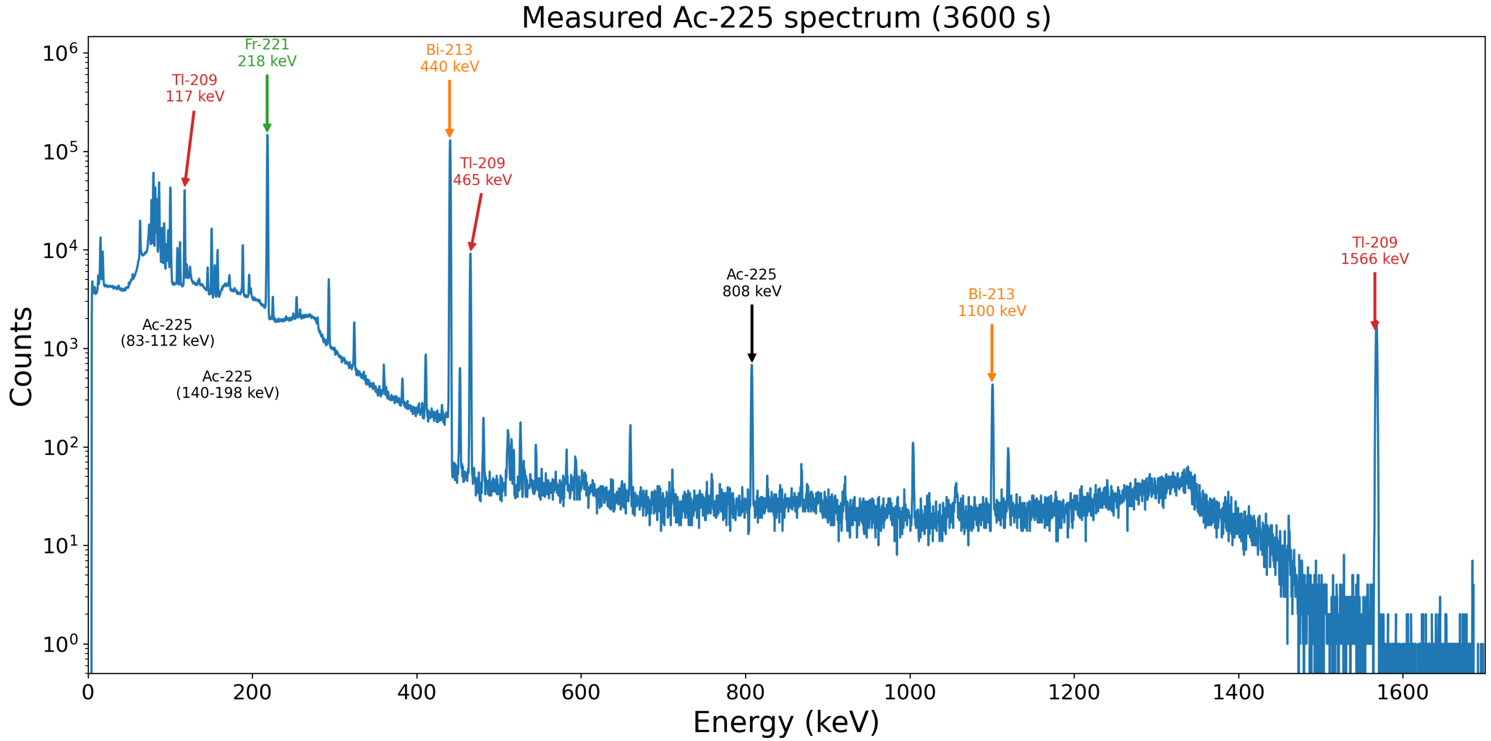
Ac-225

- *Half life: 9.9172 days*
- *Alpha decay, 4 α + 2 β^- decays until reaching semi-stable Bi-209*
- *More complicated spectrum than Lu-177*
- *Possible impurities include Ra-225, Ra-224*





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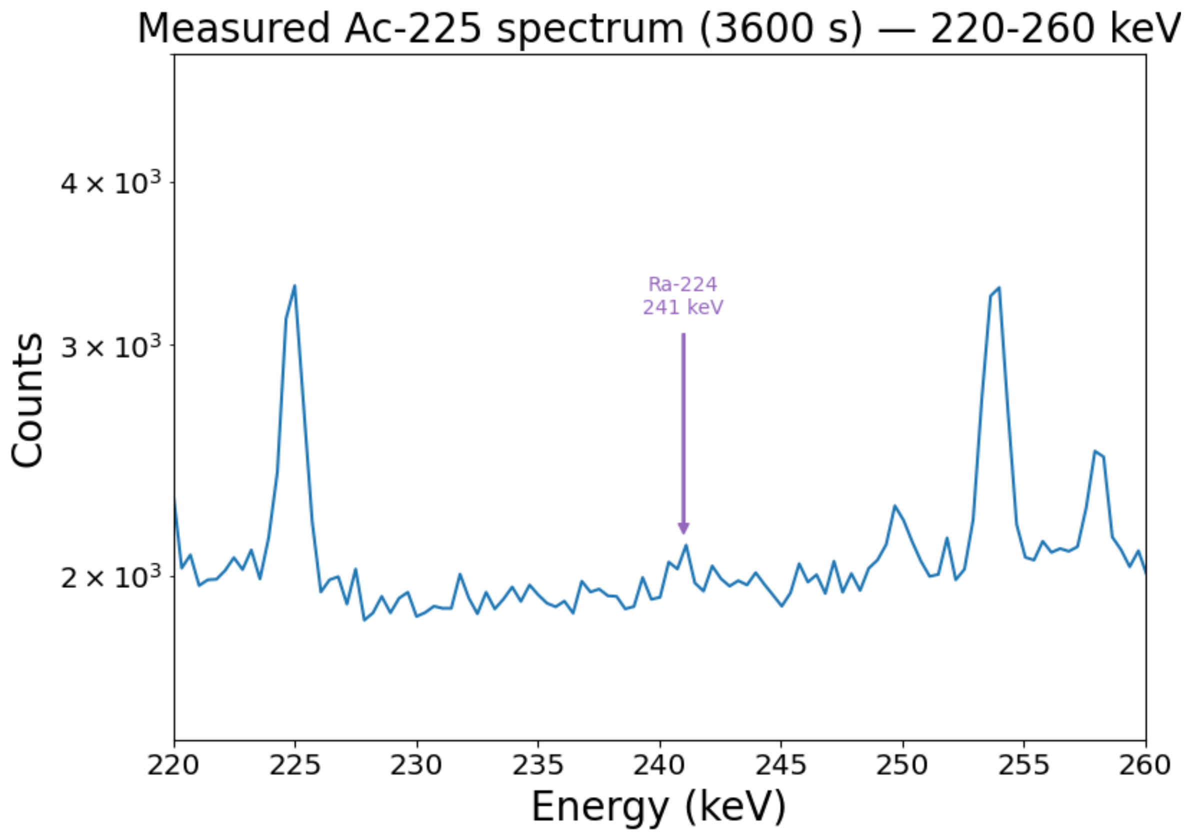
Ra-224 impurity

What's going on here?

Is there an impurity there?



^{224}Ra - Decay data

Data | Emissions | Tools | Radioactive chain | Scheme

Emissions

X and gamma emissions (**10** lines) sorted by increasing energy

Energy (keV)	Intensity (%)	Type	Origin*	Levels Start*	Levels End*
13.7085 (-)	0.373 (16)	X_L	Rn		
81.07 (-)	0.130 (3)	$X_{K\alpha2}$	Rn		
83.78 (-)	0.214 (4)	$X_{K\alpha1}$	Rn		
94.8547 (-)	0.0743 (18)	$X_{K\beta1}$	Rn		
97.8967 (-)	0.0238 (7)	$X_{K\beta2}$	Rn		
240.986 (6)	4.12 (4)	γ	Rn-220	1	0
292.7 (1)	0.0063 (7)	γ	Rn-220	2	1
404.45 (9)	0.0022 (5)	γ	Rn-220	3	1
422.04 (10)	0.0030 (5)	γ	Rn-220	4	1
645.44 (9)	0.0054 (9)	γ	Rn-220	3	0

^{225}Ac - Decay data

Data | Emissions | Tools | Radioactive chain | Scheme

Emissions

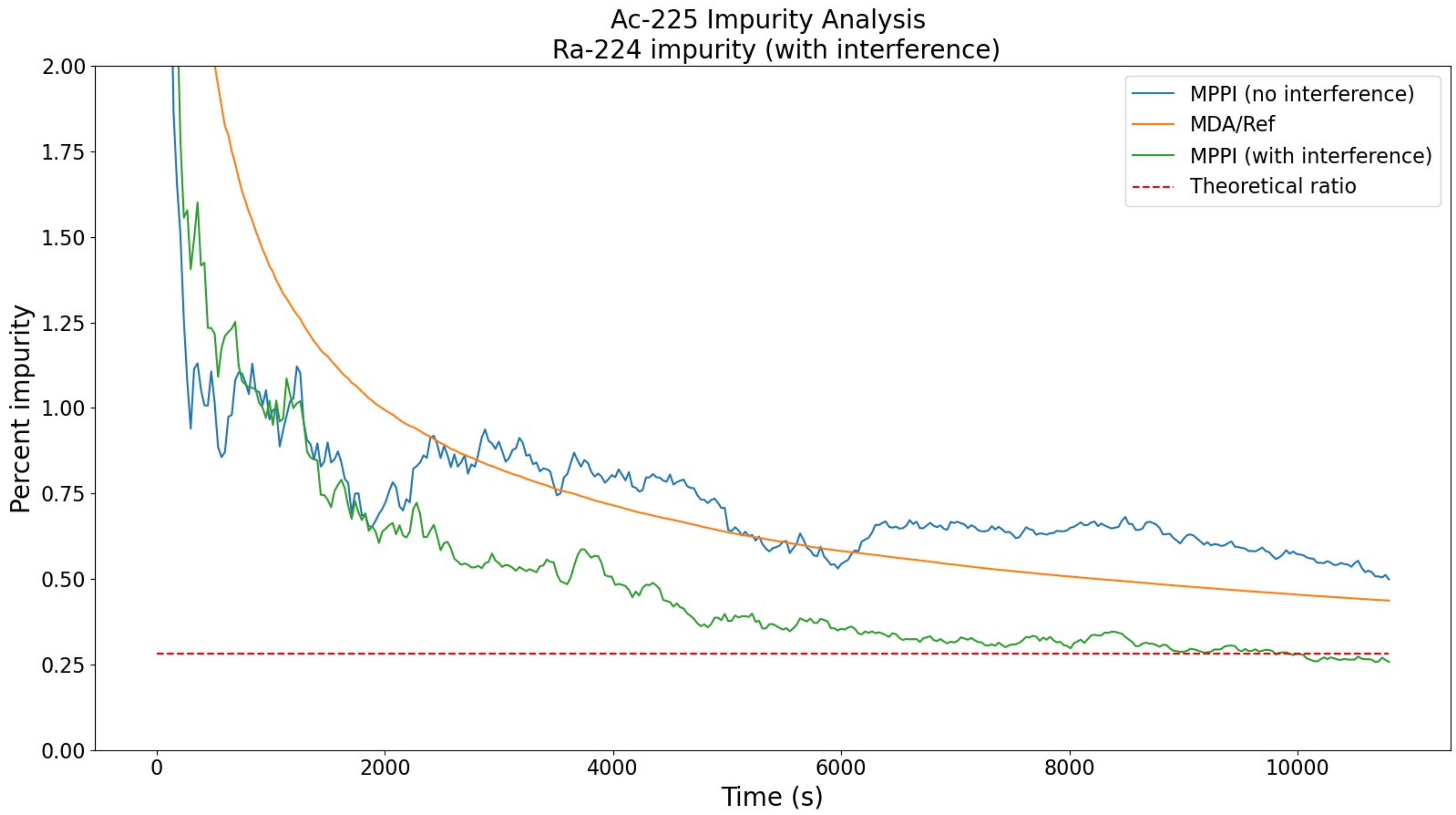
X and gamma emissions (**145** lines) sorted by increasing energy

Energy (keV)	Intensity (%)	Type	Origin*	Levels Start*	Levels End*
227.695 (21)	0.0046 (12)	γ	Fr-221	13	1
231.196 (39)	0.005 (3)	γ	Fr-221	41	32
234.49 (7)	0.0017 (3)	γ	Fr-221	14	2
238.64 (8)	0.0010 (3)	γ	Fr-221	20	4
240.663 (21)	0.0117 (10)	γ	Fr-221	15	3
243.237 (22)	0.0031 (4)	γ	Fr-221	23	9
249.614 (32)	0.0135 (10)	γ	Fr-221	16	3
253.551 (12)	0.132 (8)	γ	Fr-221	13	0

Theoretical limit without interference:

$$\frac{I_{Ac225}}{I_{Ra224}} * 100 = 0.283\%$$

Ra-224 impurity – interference corrected



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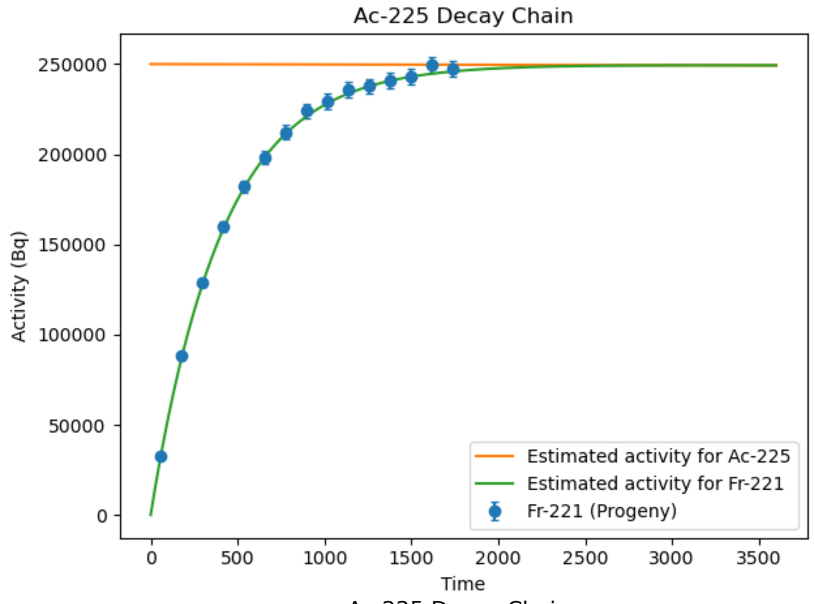
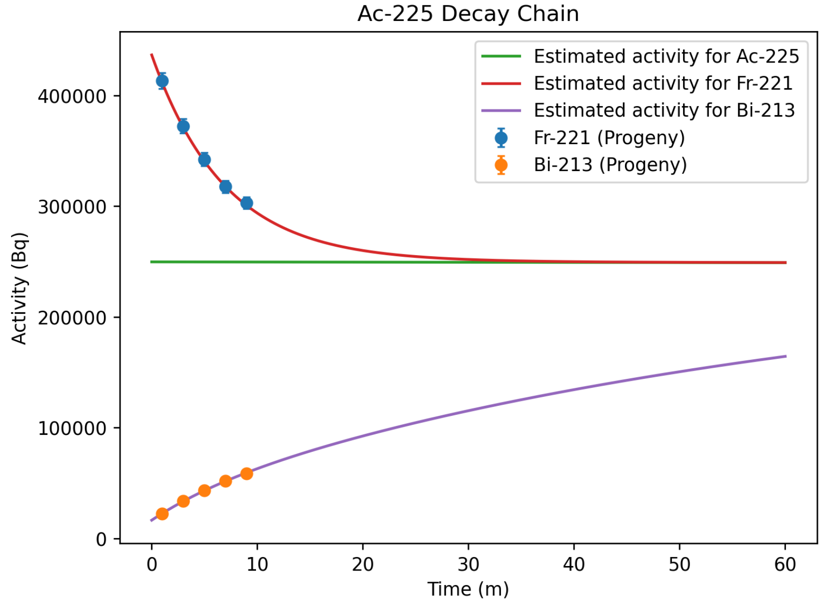
Time dependence

Progenitor activity from progeny

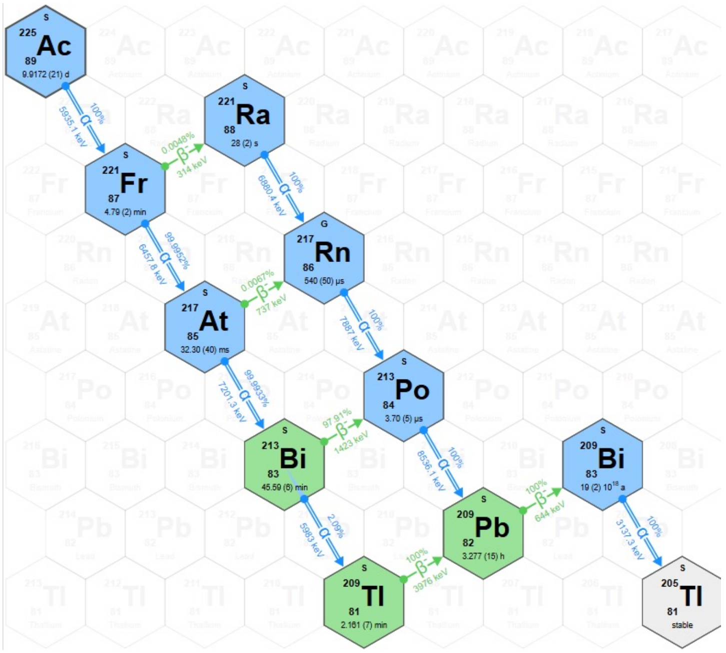
- Sometimes it is challenging to measure the activity of progenitor directly
- Measure the progeny multiple times and fit the initial activities of all* the radionuclides in the decay chain using the Bateman equation
  - All means radionuclides with half-life on the order of the measurement time
- Works for any number of generation and branching and no assumption on initial activities.

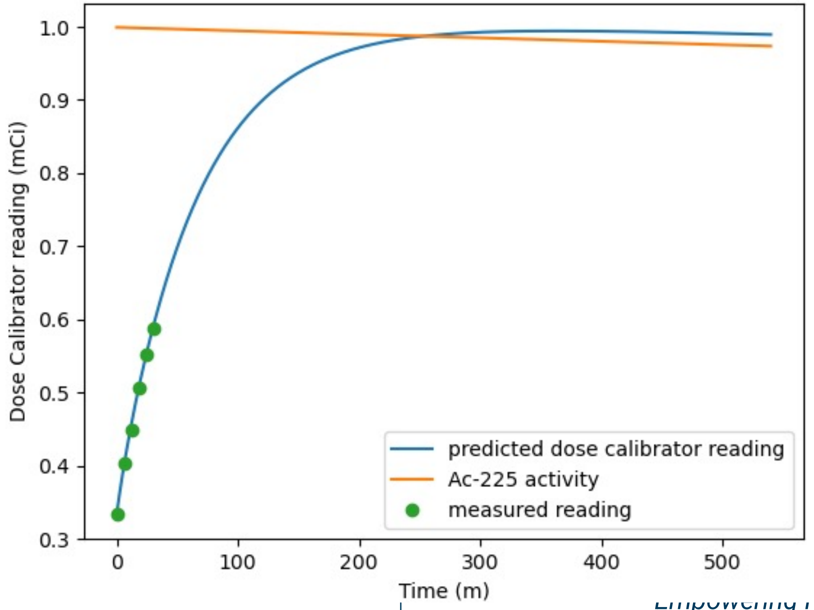




Non-spectroscopic application
Dose calibrator

- *Measures current produced in the gas of the dose calibrator*
- *Sum of the responses produced from all radionuclides in sample*
- *Need to wait for equilibrium to use the calibration factor*
- *Geant4 Monte-Carlo to predict individual responses*
- *Make 6 readings in 30 minutes is enough to fit all necessary initial activities to get the Ac-225 activity to within 2%.*





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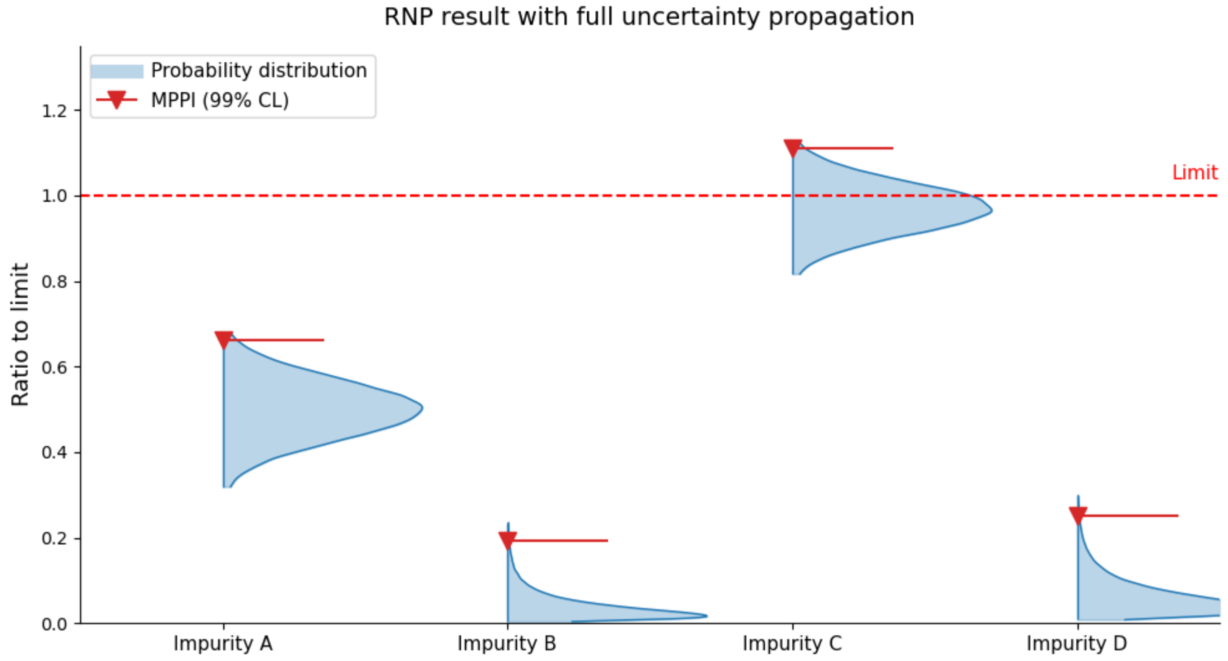
Conclusion

- Mirion provide a method for calculating the Radionuclidic purity that is defensible, takes uncertainties into account, and works when the radionuclide is and isn't identified.
  - Works for many cases – even when nature complicates things.
- It can shorten measurement time, allow you to use less activity, or reach lower impurities
- You can focus on the things that you do best.



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Thank you

A New Algorithm: The Math

THE CUMULATIVE DISTRIBUTION FOR IMPURITY ACTIVITY RATIO

The ratio Z of two normal distributions X and Y is

$$Z = \frac{X}{Y} = \frac{N_X(\mu_X, \sigma_X)}{N_Y(\mu_Y, \sigma_Y)}$$

The ratio can only be approximated with a normal distribution under certain conditions, not necessary fulfilled in these measurements. The full solution is

$$f_Z^*\left(z|\mu_x, \sigma_{u_x}, \mu_y, \sigma_{\mu_y}\right) = \frac{b(z)d(z)}{a^3(z)} \frac{1}{\sqrt{2\pi}\sigma_x\sigma_y}\left(\Phi\left(\frac{b(z)}{a(z)}\right) - \Phi\left(\frac{b(z)}{a(z)}\right)\right) + \frac{1}{a^2(z)\pi\sigma_x\sigma_y} e^{-\frac{c}{2}}$$

$$a(z) = \sqrt{\frac{1}{\sigma_x^2}z^2 + \frac{1}{\sigma_y^2}}, b(z) = \frac{\mu_x}{\sigma_x^2}z + \frac{\mu_y}{\sigma_y^2}, c(z) = \frac{\mu_x^2}{\sigma_x^2} + \frac{\mu_y^2}{\sigma_y^2}, d(z) = e^{\frac{b^2(z) - ca^2(z)}{2a^2(z)}}$$

It is another probability distribution that in the "simple" form has the probability distribution function PDF

$$f_Z^\dagger(z|\mu_x, \sigma_{u_x}, \mu_y, \sigma_{\mu_y}) = \frac{1}{\sqrt{\pi}} \frac{p}{\operatorname{erf}(q)} \frac{1}{r} \frac{1 + \frac{p^2}{q^2}\frac{z}{r}}{\left(1 + \frac{p^2}{q^2}\frac{z^2}{r^2}\right)^{\frac{3}{2}}} e^{-\frac{p^2\left(\frac{z}{r}-1\right)^2}{1+\frac{p^2 z^2}{q^2 r^2}}}$$

$$p = \frac{\mu_X}{\sqrt{2}\sigma_X}, q = \frac{\mu_Y}{\sqrt{2}\sigma_Y}, r = \frac{\mu_X}{\mu_Y}$$

And the cumulative distribution function CDF is

$$F_Z^\dagger\left(z_0|\mu_x, \sigma_{u_x}, \mu_y, \sigma_{\mu_y}\right) = f\left(z < z_0|\mu_x, \sigma_{u_x}, \mu_y, \sigma_{\mu_y}\right) = \frac{1}{2}\left(1 + \frac{\operatorname{erf}\left(\frac{p\left(\frac{z_0}{r} - 1\right)}{\sqrt{1 + \frac{p^2}{q^2}\frac{z_0^2}{r^2}}}\right)}{\operatorname{erf}(q)}\right)$$

EVALUATING AN MPPI

Following the steps in ISO11929, Non-negative prior distribution

$$f_Z(z|Z \geq 0) = H(z) = \begin{cases} 1 & (z \geq 0) \\ 0 & (z < 0) \end{cases}$$

Multiply it and renormalize

$$f_Z\left(z\middle|\mu_x, \sigma_{u_x}, \mu_y, \sigma_{\mu_y}, Z \geq 0\right) = N f_Z\left(z\middle|\mu_x, \sigma_{u_x}, \mu_y, \sigma_{\mu_y}\right) f_Z(z|Z \geq 0)$$

Normalization factor

$$N = \frac{1}{\int_0^{z=\infty} f_Z dz} = \frac{1}{1 - \int_{z=-\infty}^0 f_Z dz} = \frac{1}{1 - F(0)}$$

Probability density and cumulative distribution function

$$f_Z\left(z\middle|\mu_x, \sigma_{u_x}, \mu_y, \sigma_{\mu_y}, Z \geq 0\right) = \begin{cases} \frac{f_Z}{1 - F_Z(0)} & z \geq 0 \\ 0 & z < 0 \end{cases},$$

$$F_Z(z_0|\mu_x, \sigma_{u_x}, \mu_y, \sigma_{\mu_y}, Z \geq 0) = \begin{cases} \frac{F_Z(z_0) - F_Z(0)}{1 - F_Z(0)} & z_0 \geq 0 \\ 0 & z_0 < 0 \end{cases}$$

MPPI

$$\int_{z=0}^{\mathrm{MPPI}} \frac{f_Z}{1 - F_Z(0)} dz = \frac{F_Z(\mathrm{MPPI}) - F_Z(0)}{1 - F_Z(0)} = 1 - \alpha$$

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