Recent *Activities* of the NIST Nuclear Medicine Program

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National Institute of Standards and Technology
U.S. Department of Commerce

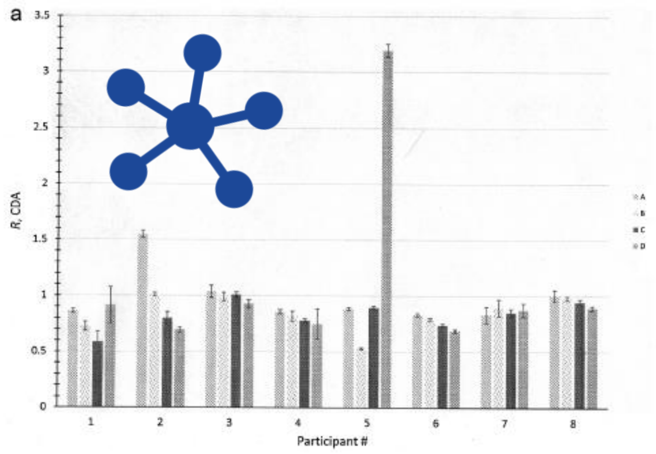
PHYSICAL MEASUREMENT LABORATORY

The becquerel in nuclear medicine

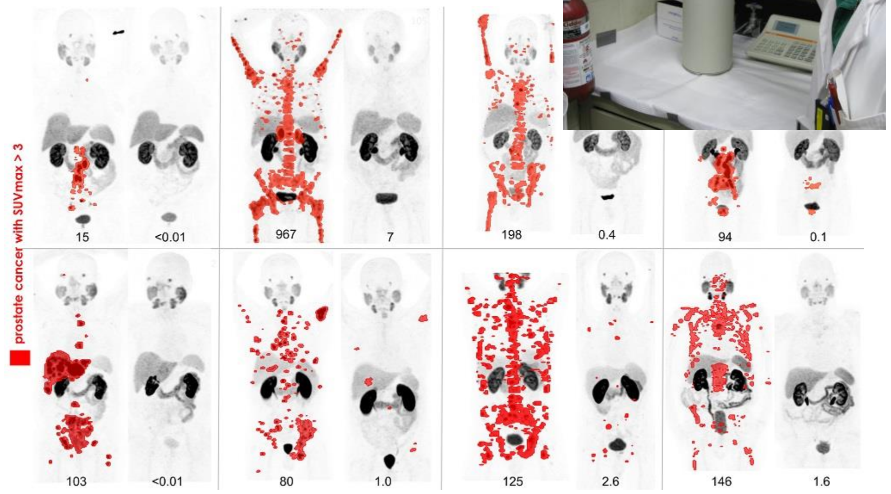
NIST

Precision measurements of activity are the foundation for:

- Reliable administration of patient dosages
- Quantitative molecular imaging
- Personalized dosimetry
- Multicenter trials



Zimmerman et al., Z. Med. Phys. 27 (2017) 98.

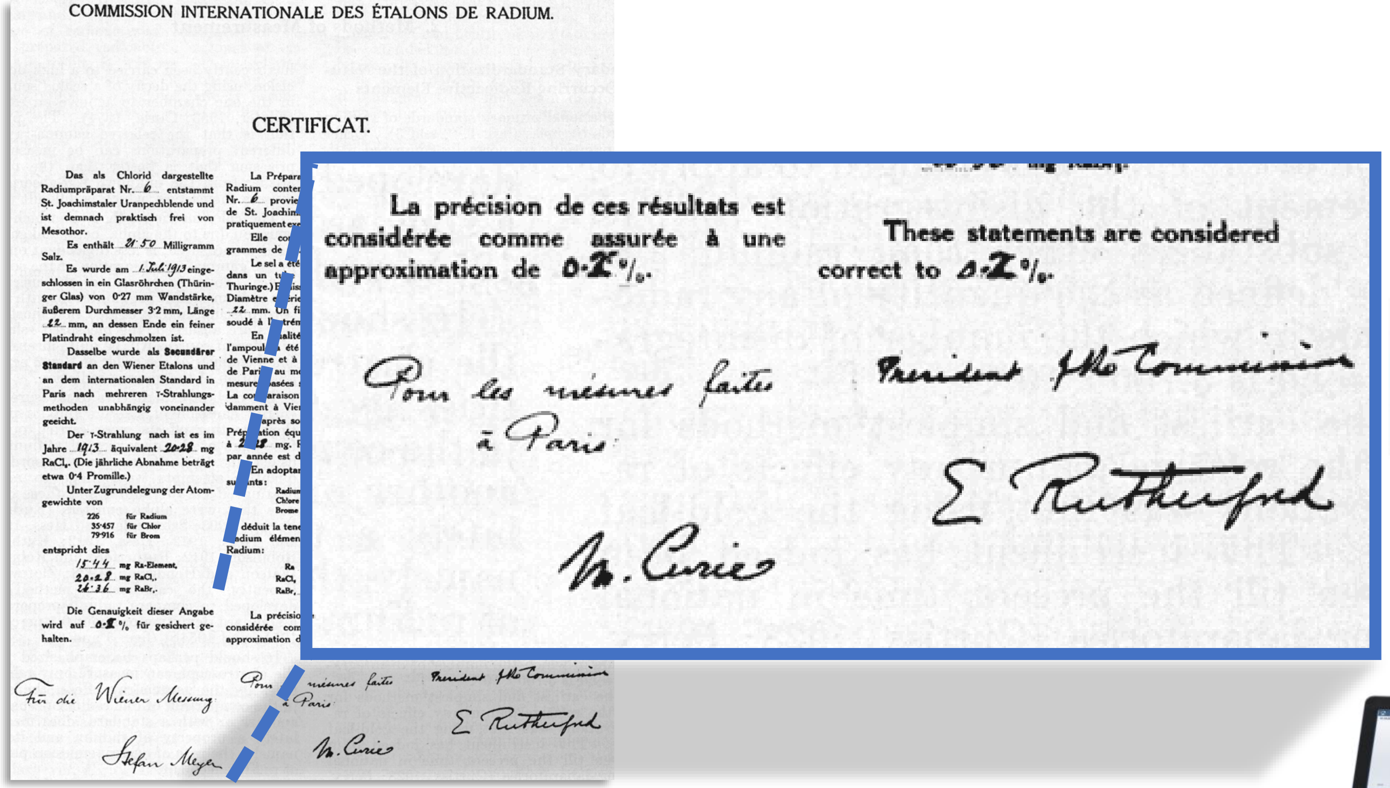


https://www.snmmi.org/NewsPublications/NewsDetail.aspx?ItemNumber=29483

https://images.app.goo.gl/DEytSwNtUHjsYsov6

Radionuclide metrology for medicine

NIST was measuring activity before there was a Bq. And there's always been a focus on medical applications.



COMMISSION INTERNATIONALE DES ÉTALONS DE RADIUM.

CERTIFICAT.

Das als Chlorid dargestellte Radiumpräparat Nr. 6 entstammt St. Joachimstaler Uranpechblende und ist demnach praktisch frei von Mesothor.

Es enthält 21·50 Milligramm Salz.

Es wurde am 1. Juli 1913 eingeschlossen in ein Glasröhrchen (Thüringer Glas) von 0·27 mm Wandstärke, äußerem Durchmesser 3·2 mm, Länge 22 mm, an dessen Ende ein feiner Platindraht eingeschmolzen ist.

Dasselbe wurde als **Secundärer Standard** an den Wiener Etalons und an dem internationalen Standard in Paris nach mehreren γ-Strahlungsmethoden unabhängig voneinander geeicht.

Der γ-Strahlung nach ist es im Jahre 1913 äquivalent 20·28 mg $RaCl_2$. (Die jährliche Abnahme beträgt etwa 0·4 Promille.)

Unter Zugrundelegung der Atomgewichte von

226 für Radium
35·457 für Chlor
79·916 für Brom

entspricht dies

15·44 mg Ra-Element,
20·28 mg $RaCl_2$,
26·36 mg $RaBr_2$.

Die Genauigkeit dieser Angabe wird auf 0·2 % für gesichert gehalten.

La précision de ces résultats est considérée comme assurée à une approximation de 0·2 %.

These statements are considered correct to 0·2 %.

Für die Wiener Messung

Stefan Meyer

Pour les mesures faites à Paris

M. Curie

President of the Commission

E Rutherford

https://www.nist.gov/blogs/taking-measure/saving-marie-curies-last-radium-standard

Quantitative Imaging Biomarkers Alliance RSNA

Xofigo® radium Ra 223 dichloride INJECTION

SNMMI SOCIETY OF NUCLEAR MEDICINE AND MOLECULAR IMAGING

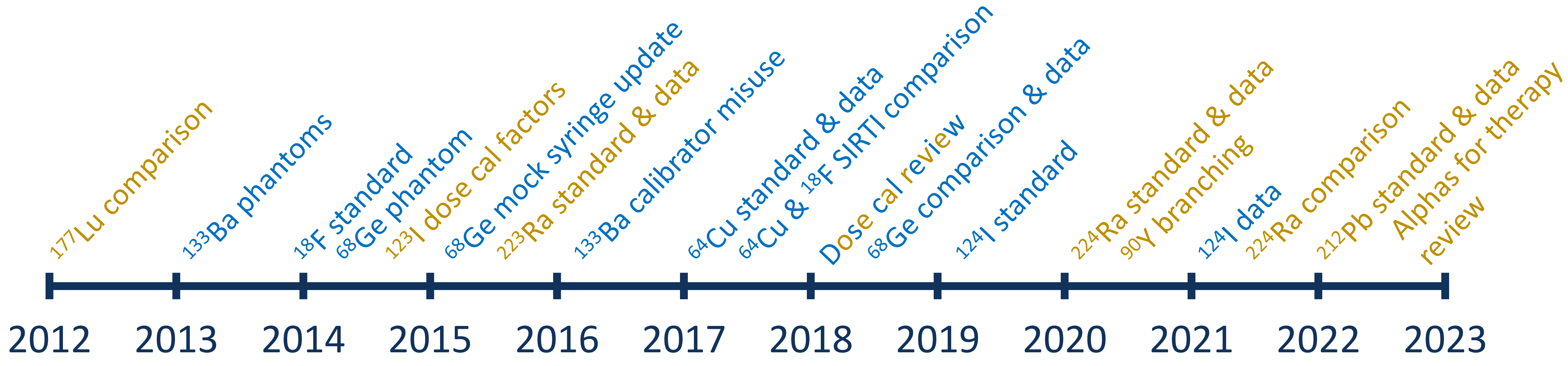
AAPM

ICRM

We’ll call the last decade “recent”

NIST

- **Imaging**
  - Challenges associated with EC branches
- **Therapy**
  - Challenges associated with decay chain nuclides



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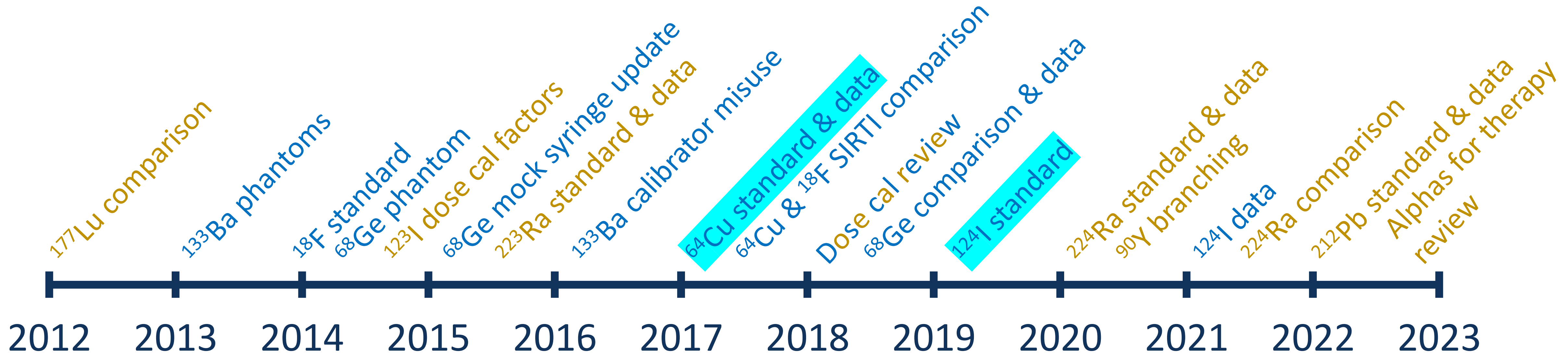

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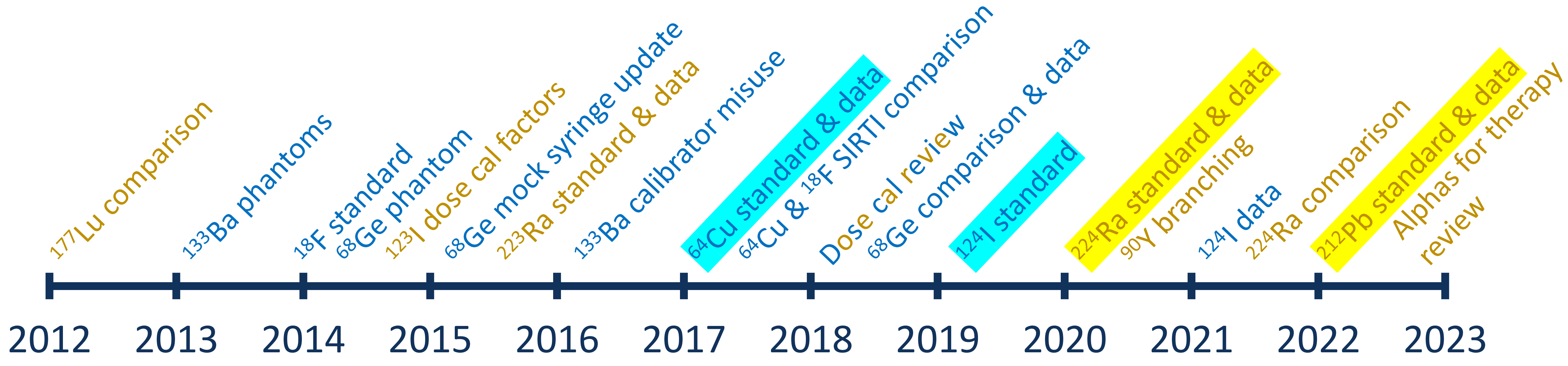

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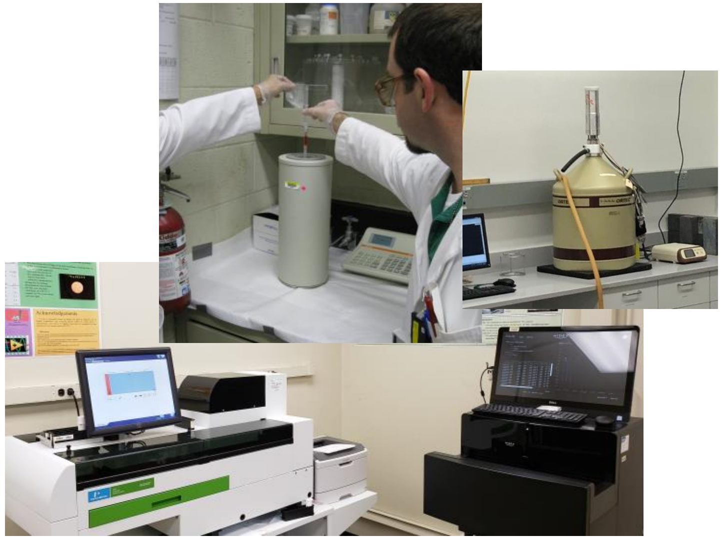
- **Imaging**
  - Challenges associated with EC branches
- **Therapy**
  - Challenges associated with decay chain nuclides
- **Dissemination**



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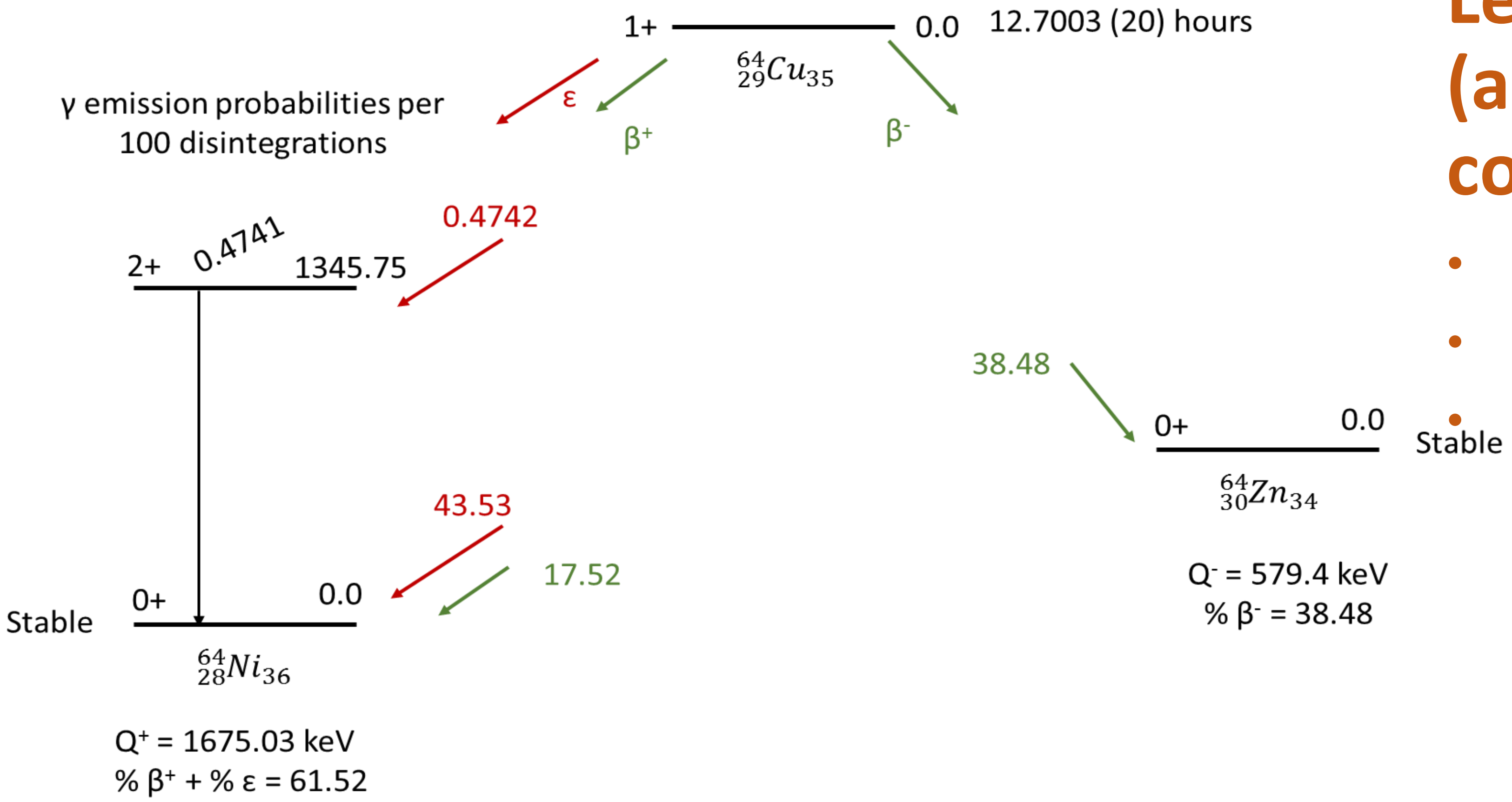
^{124}I standard
^{224}Ra standard & data
^{90}Y branching
^{124}I data
^{224}Ra comparison
^{212}Pb standard & data
Alphas for therapy review

2012 2013 2014 2015 2016 2017 2018 2019 2020 2021 2022 2023

Challenges associated with EC branches

Decay by electron capture competes with positron emission.



Let's talk about (anti)coincidence counting.

- Primary method: $N_{LS} = N_0(1 - Y)$
- Need decay to an excited state
- Corrections required when KLM capture probabilities differ between monitored and contributing EC decays

http://www.nucleide.org/DDEP_WG/Nuclides/Cu-64_tables.pdf

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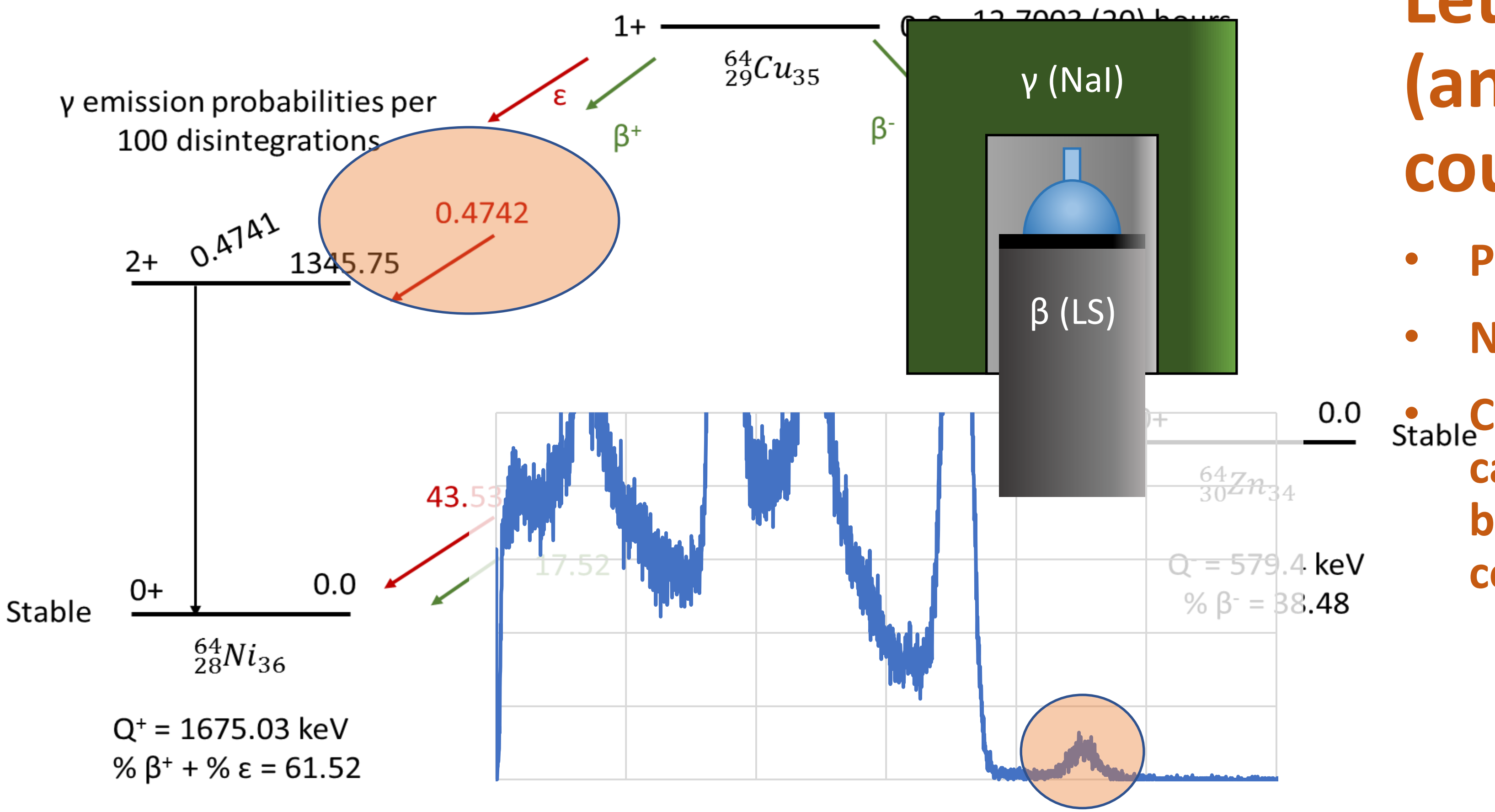

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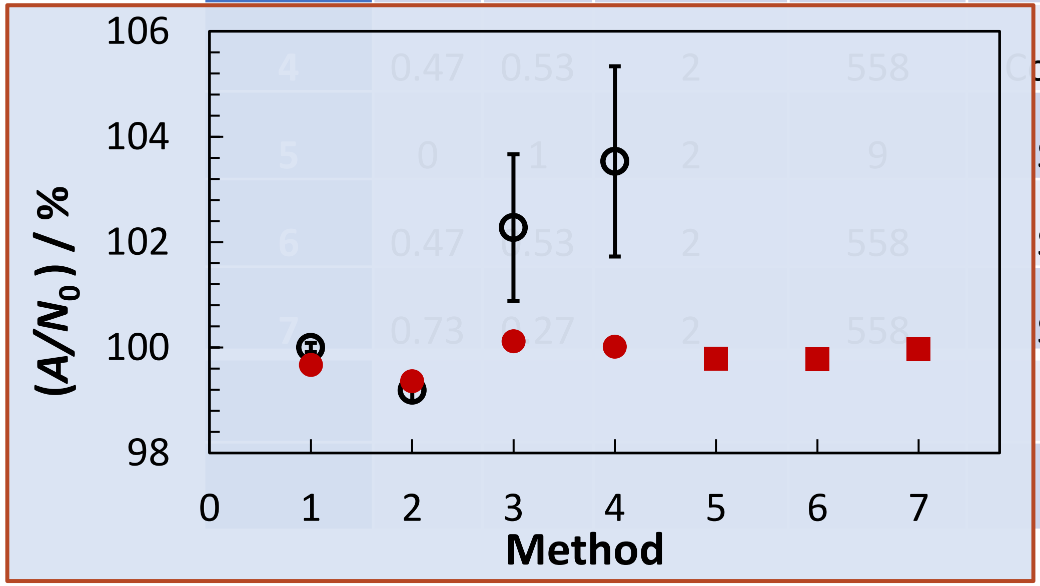
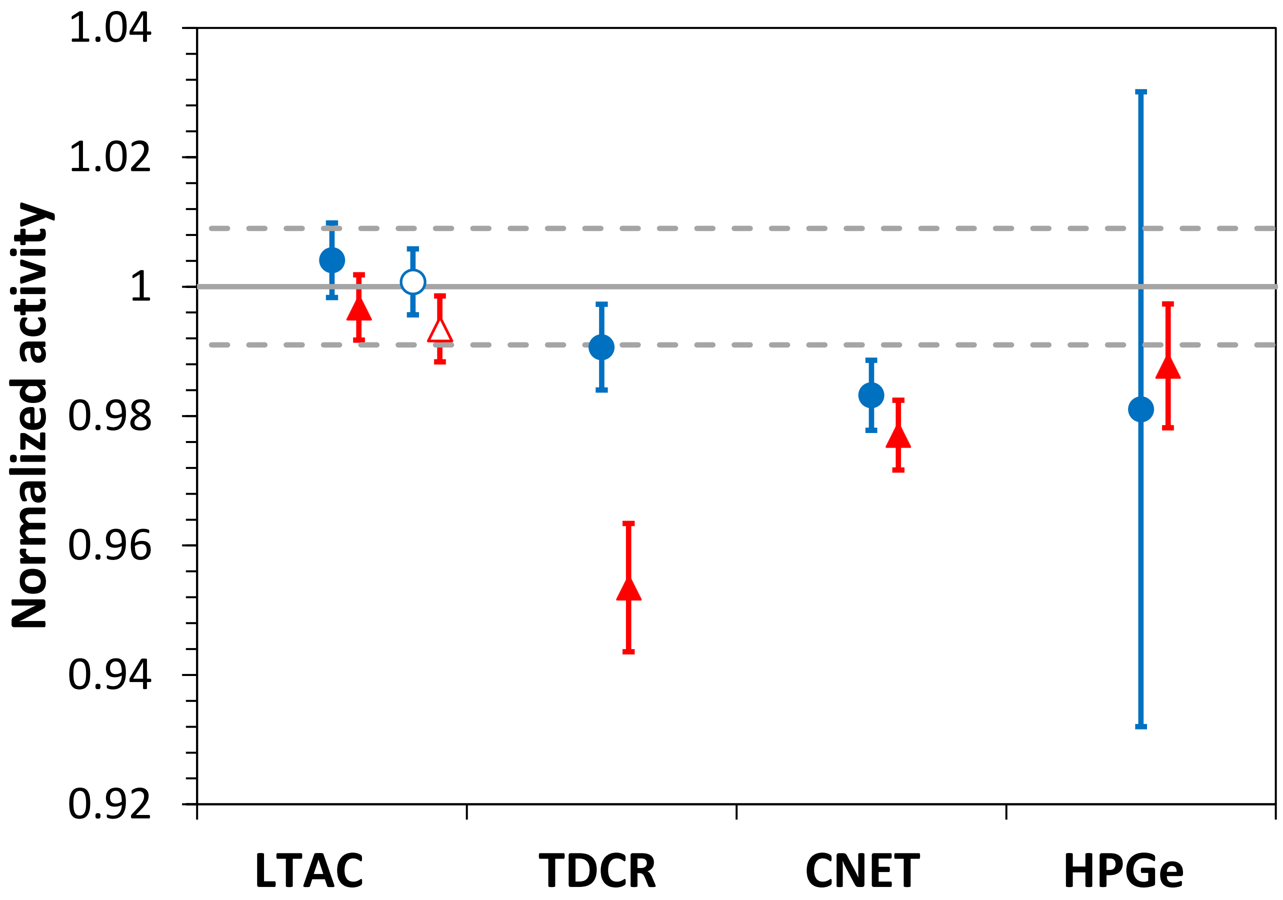
Monte Carlo corrections improve results

Method	a_2	a_3	E_{LS} Start	E_{LS} End	Description	(A/N_0) / %	F	(A'/N_0) / %	u_c / %
1	0	1	2	9	Corr. Lin	100	0.9967	99.67	0.09
2	0	1	2	9	Corr. Quad	99.19	1.0017	99.36	0.20
3	0.47	0.53	2	558	Corr. Lin	102.27	0.9789	100.12	1.39
4	0.47	0.53	2	558	Corr. Quad	103.53	0.9660	100.01	1.80
5	0	1	2	9	Scaling	----	----	99.78	0.02
6	0.47	0.53	2	558	Scaling	----	----	99.78	0.12
7	0.73	0.27	2	558	Scaling	----	----	99.96	0.03
						100.49	**AVE**	**99.81**	
						2.01	**SD**	**0.25**	



ARI 134, 280-285 (2018).

Methods comparison – Cu-64



LTAC with Monte Carlo correction adopted as primary standard.

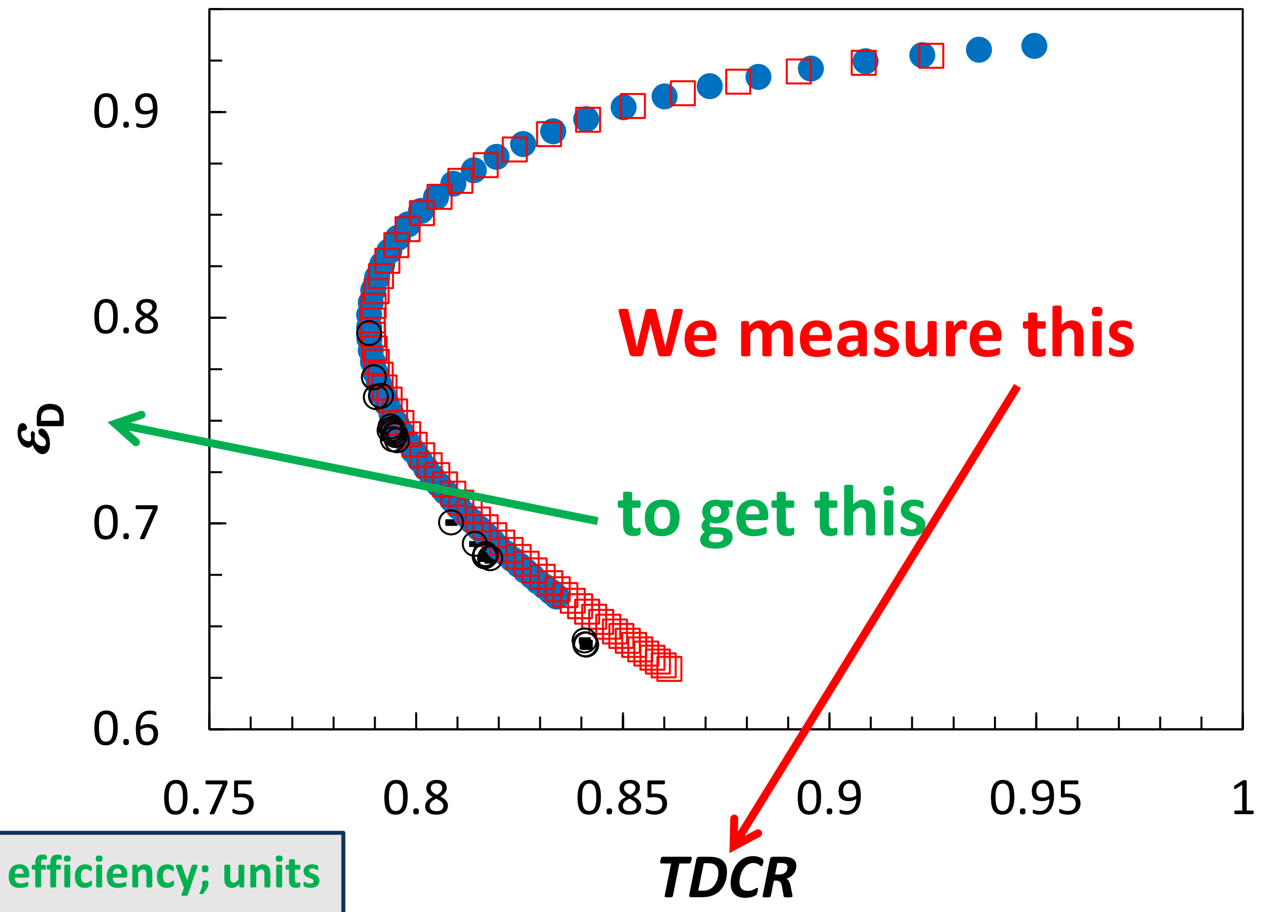
Radionuclide calibrator settings published.

Gamma-ray emission intensities re-evaluated.

Difficulties with figure-of-merit based model observed.

ARI 134, 280-285 (2018); 139, 266-273 (2018); 129, 6-12 (2017).

Methods comparison – Cu-64



ε = efficiency; units "counts per decay"

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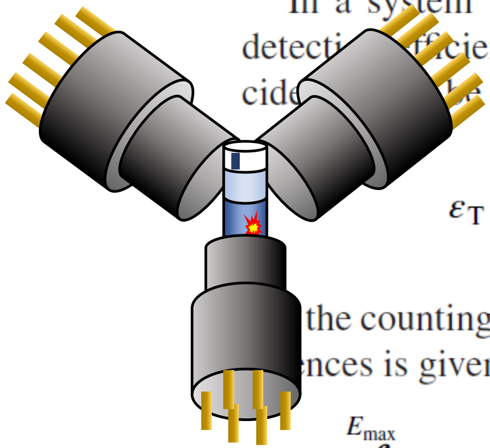
EC branches and TDCR Counting



In a system with three PMT which have equal quantum detection efficiencies, the counting efficiency for triple coincidences can be calculated according to

$$\varepsilon_{\mathrm{T}} = \int_{0}^{E_{\max}} S(E)\left(1 - \mathrm{e}^{\frac{-E\cdot Q(E)}{3\cdot M}}\right)^{3} \mathrm{d}E, \qquad (3)$$

and the counting efficiency for the logical sum of double coincidences is given by

$$\varepsilon_{\mathrm{D}} = \int_{0}^{E_{\max}} S(E)\ \left(3(1 - \mathrm{e}^{-EQ(E)/3M})^{2} - 2(1 - \mathrm{e}^{-EQ(E)/3M})^{3}\right)\mathrm{d}E. \qquad (4)$$

Here also, the counting efficiencies depend on the free parameter M. The free parameter of a given LS sample is defined by the condition

$$\frac{\varepsilon_{\mathrm{T}}(M)}{\varepsilon_{\mathrm{D}}(M)} = \frac{R_{\mathrm{T}}}{R_{\mathrm{D}}}, \qquad (5)$$

where R_{T} and R_{D} are the experimentally determined net counting rates in the triple and the double channels, respectively. After determination of the free parameter, the counting

Metrologia 52, S172-S190 (2015).

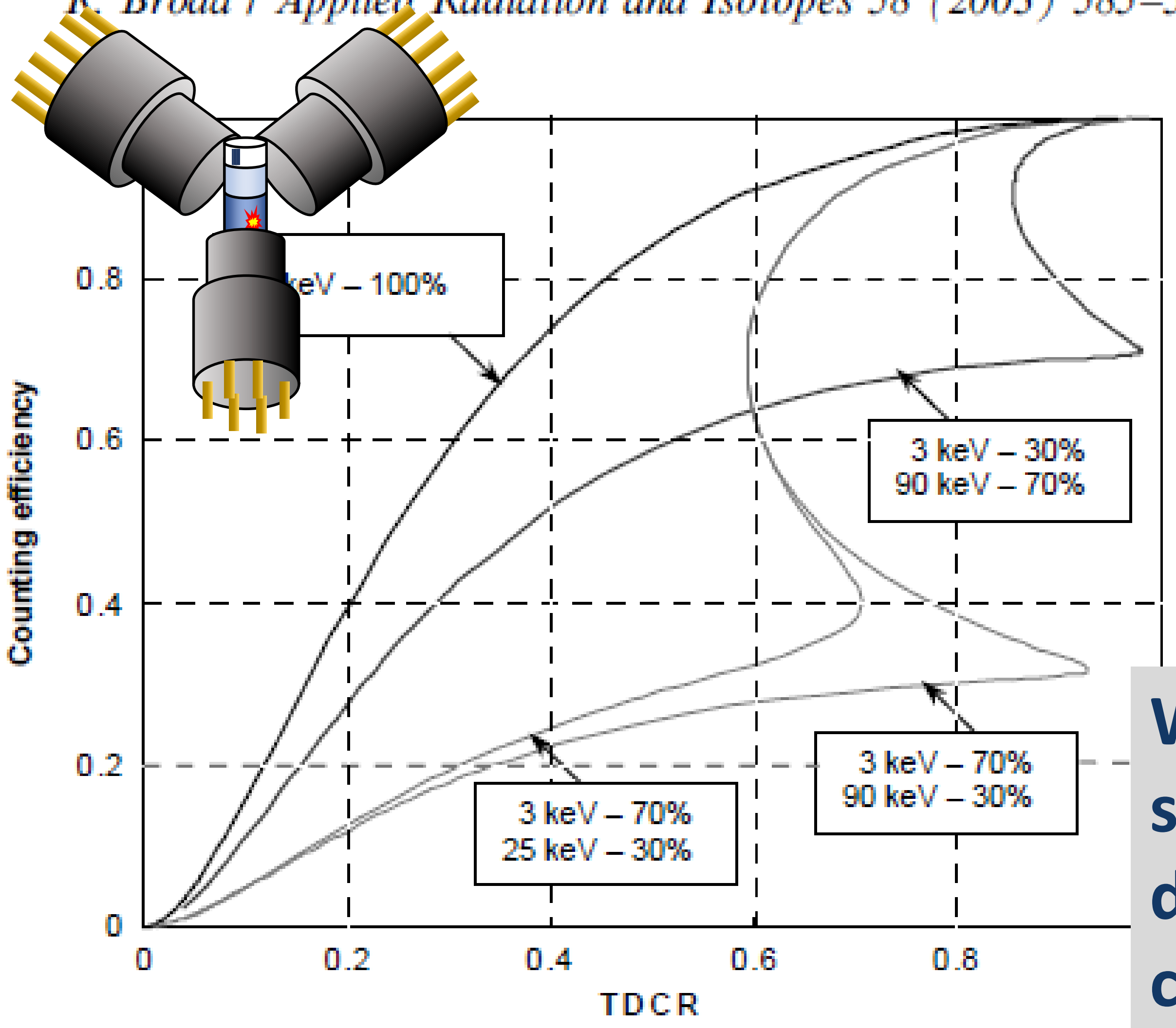
Let’s talk about tiple-to-double coincidence ratio counting.

- Primary method
- Liquid scintillation counting
- Discreet electron energies from EC decays make things tricky

Efficiencies depend on the energy spectrum and the energy-dependent quench function

EC branches and TDCR Counting

R. Broda / Applied Radiation and Isotopes 58 (2003) 585–594



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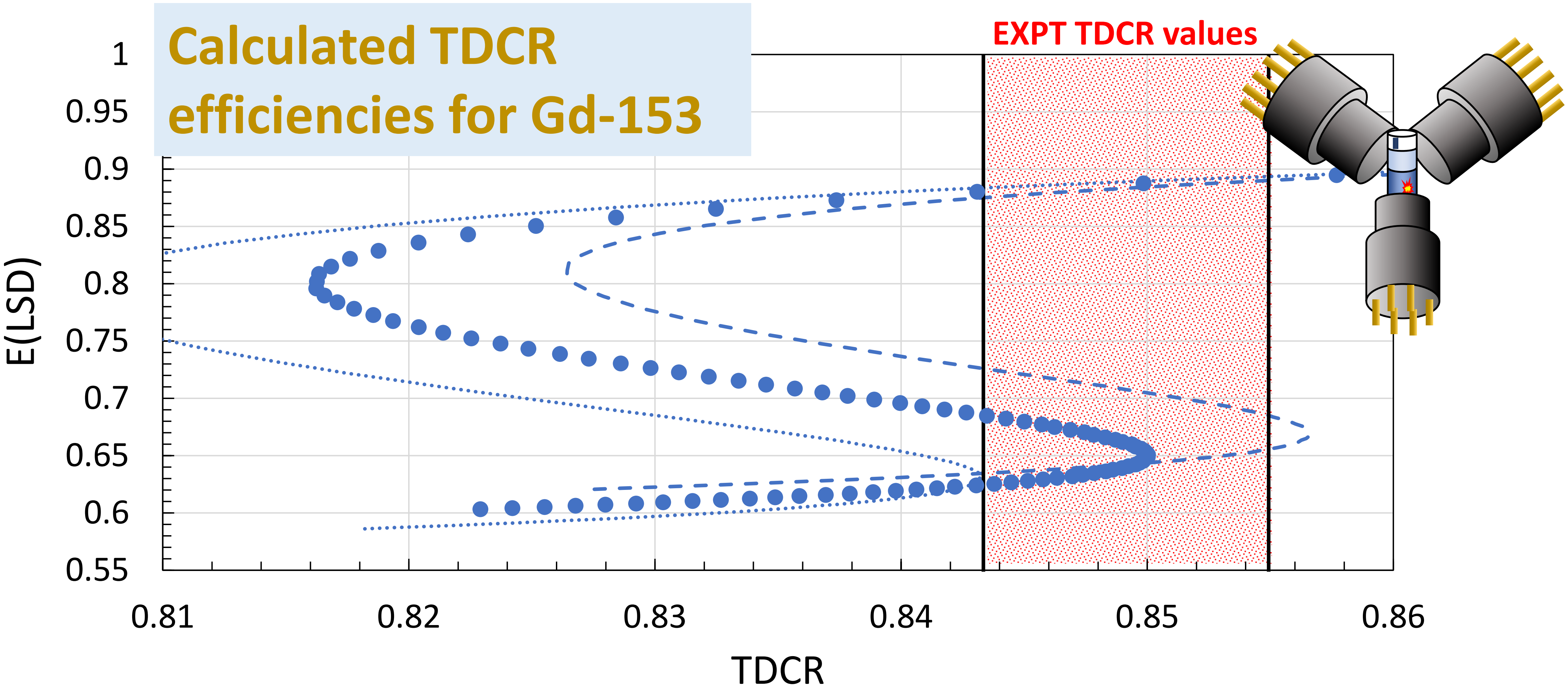
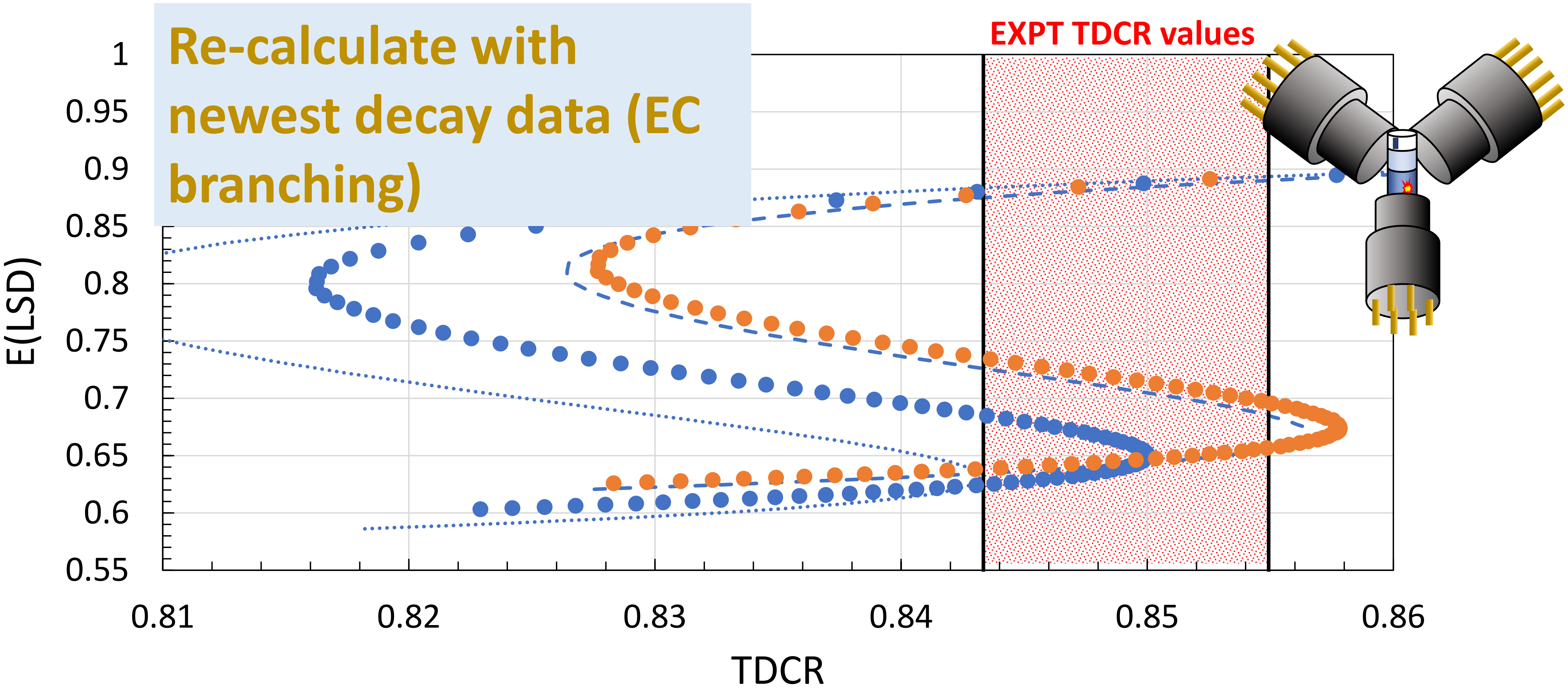
With discreet peaks in the energy spectrum, the weights of the peaks dictate the shape of the efficiency curves.

An example of TDCR with EC

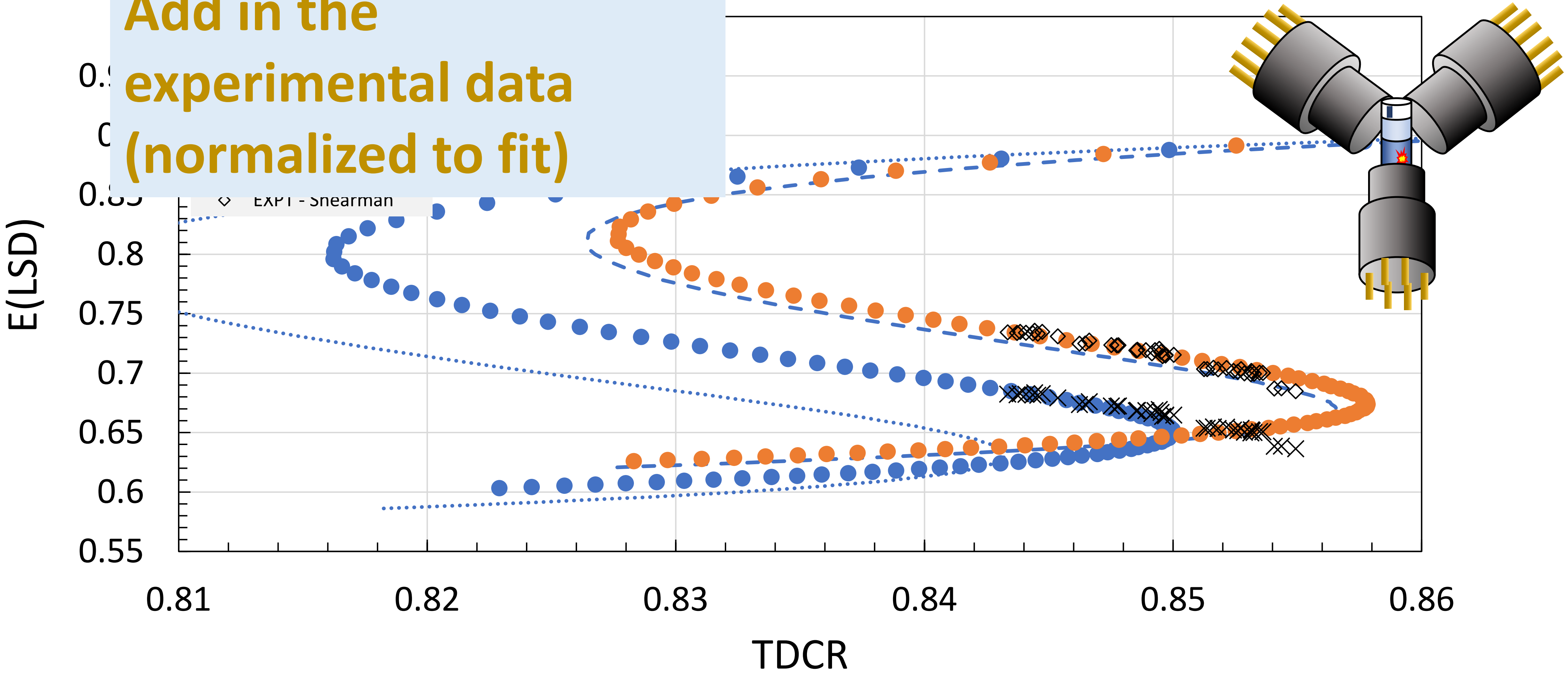


An example of TDCR with EC

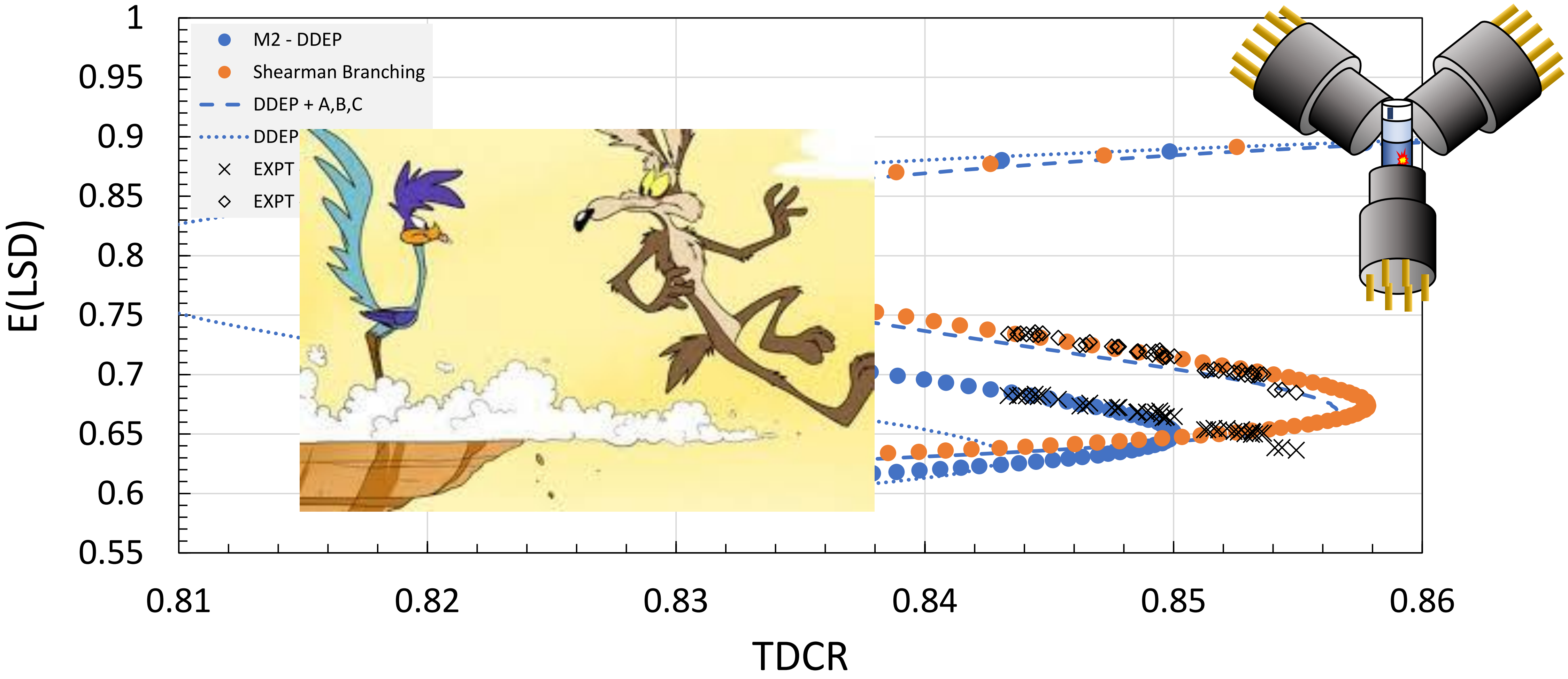


An example of TDCR with EC

Add in the experimental data (normalized to fit)



An example of TDCR with EC

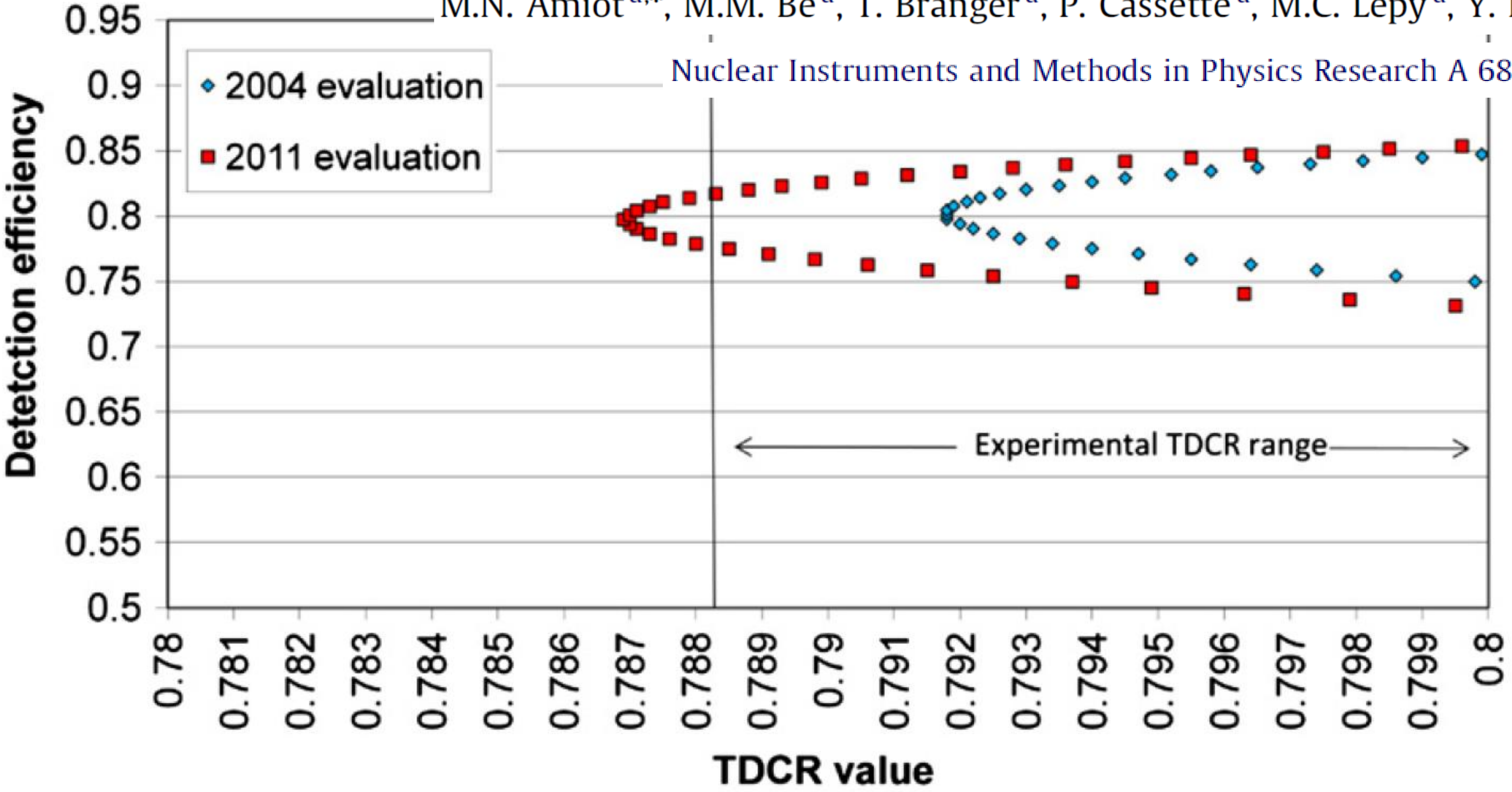


Wile E. Coyote & Cu-64

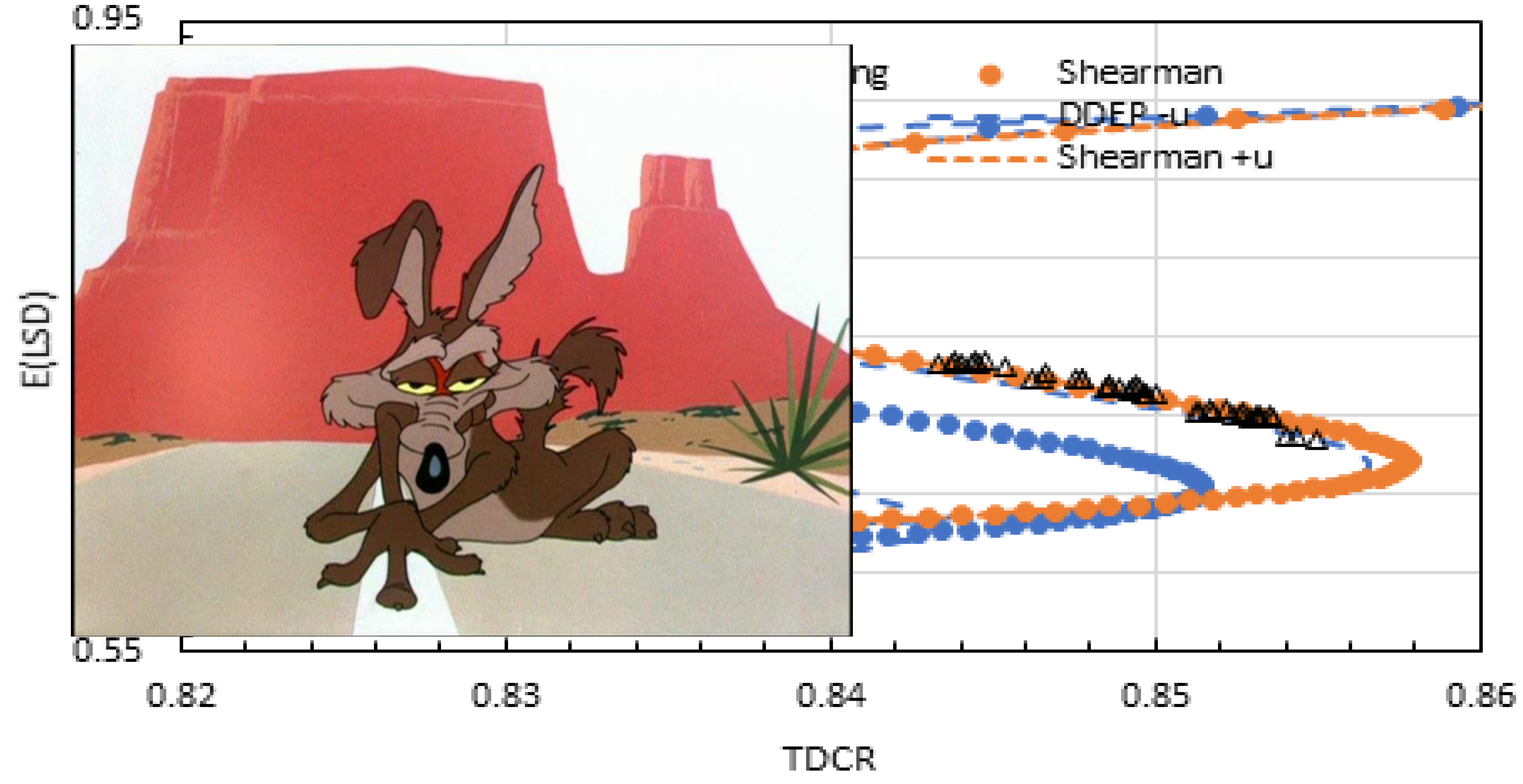
Standardization of ^{64}Cu using an improved decay scheme

M.N. Amiot[a,*], M.M. Bé[a], T. Branger[a], P. Cassette[a], M.C. Lépy[a], Y. Ménesguen[a], I. Da Silva[b]

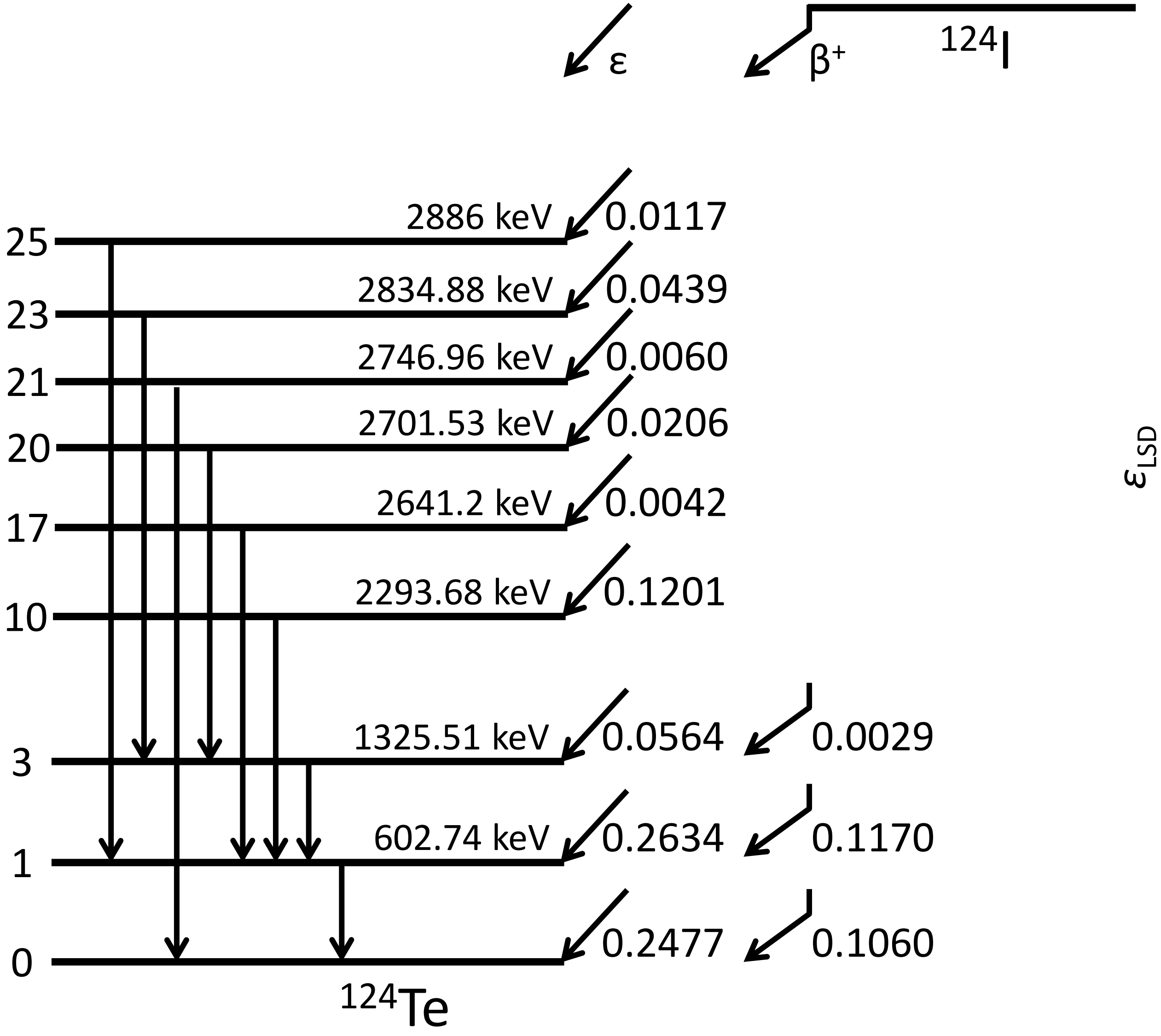
Nuclear Instruments and Methods in Physics Research A 684 (2012) 97–104

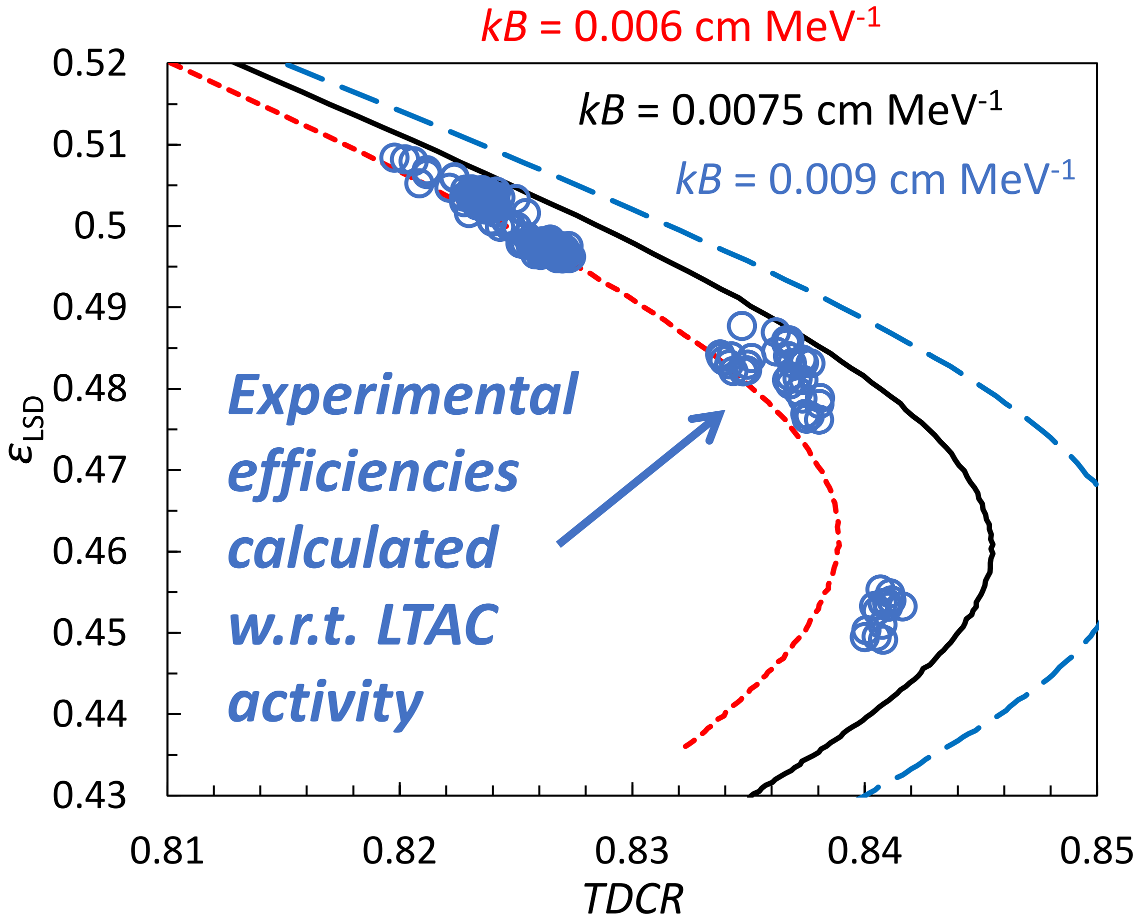


LTAC works, TDCR comments on branching



Wile E. Coyote & I-124

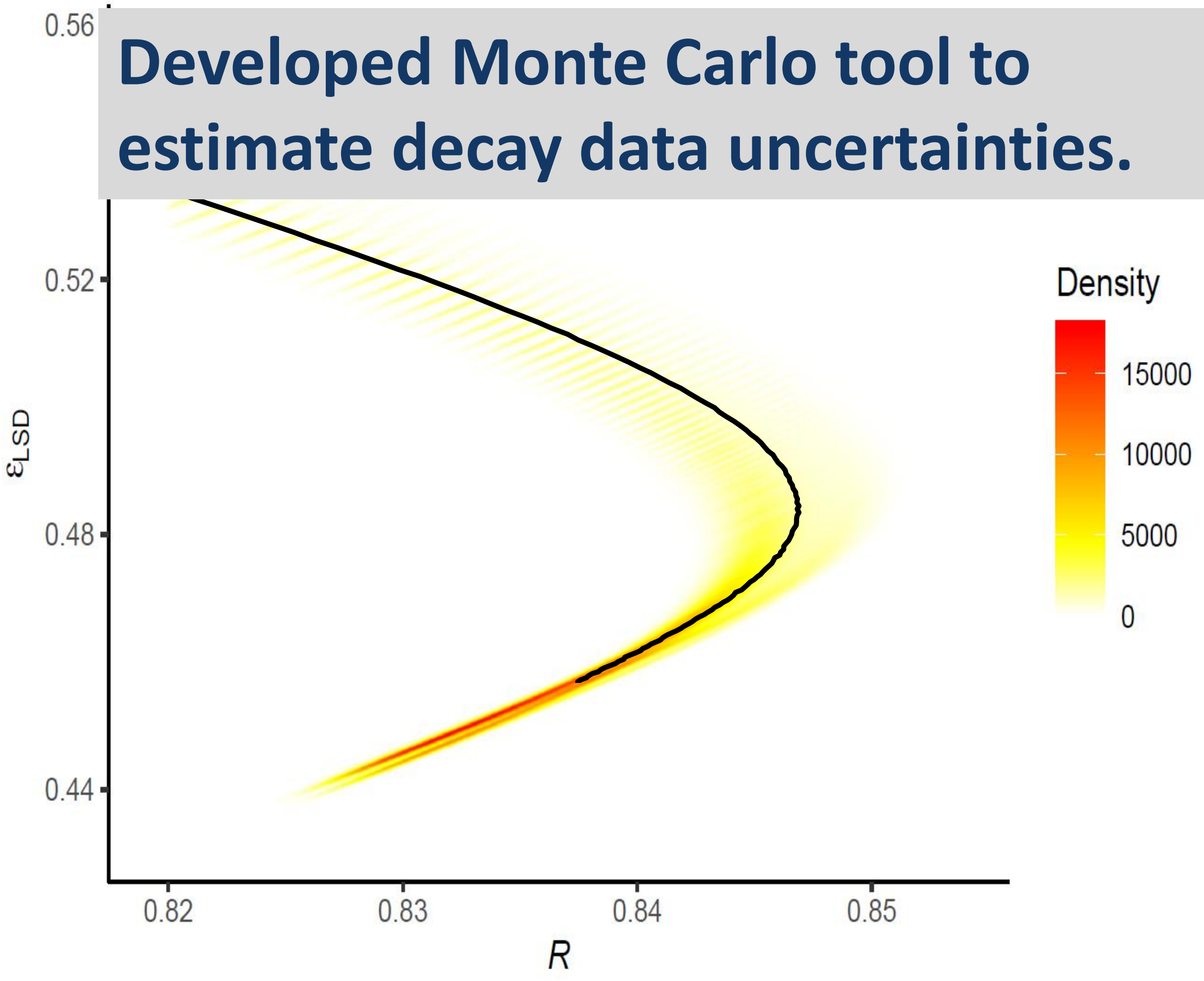


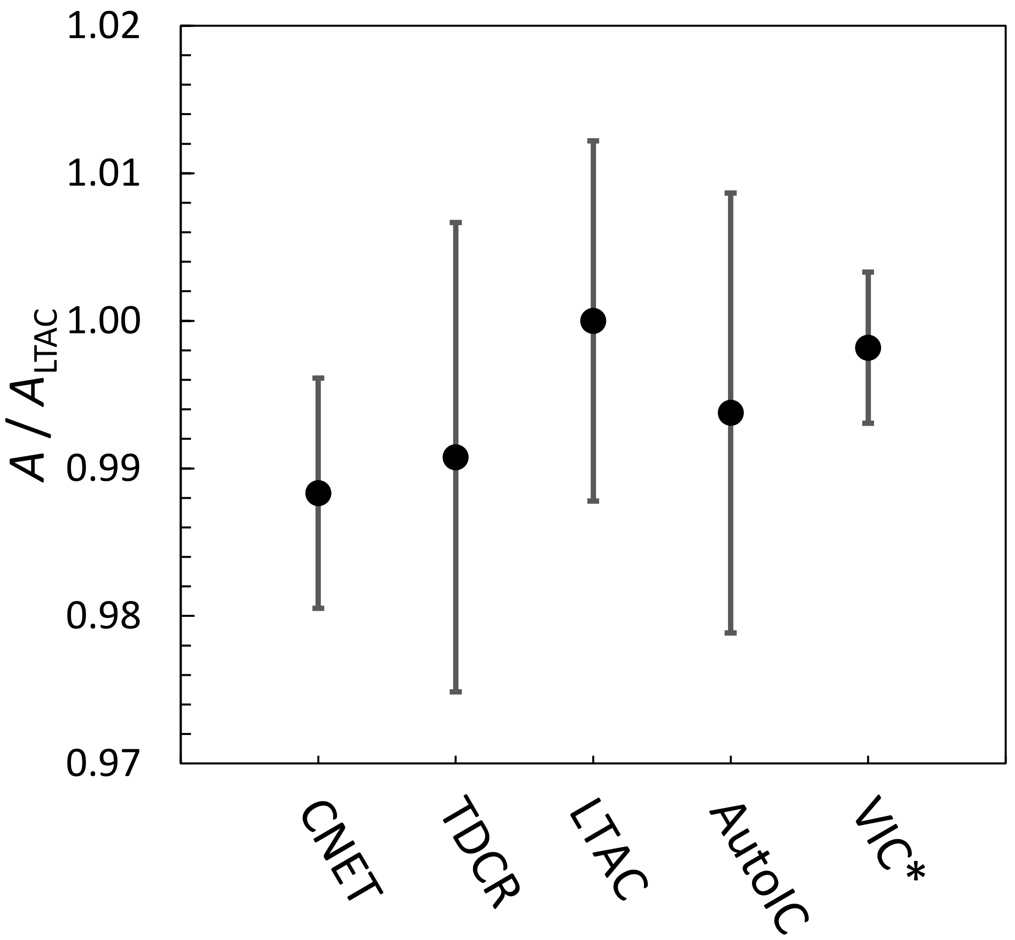


ARI 154, 108849 (2019).

Dealing with EC

Developed Monte Carlo tool to estimate decay data uncertainties.





ARI 154, 108849 (2019).

Meeting the EC challenges

NIST

Always use multiple methods and design measurements to reduce sensitivity to decay data uncertainties

Work for improved decay data

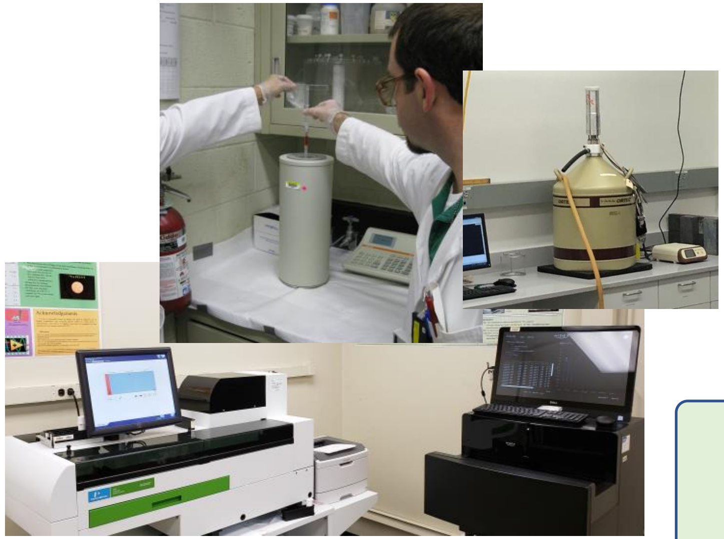
Work for improved efficiency models

Realistic uncertainty estimates

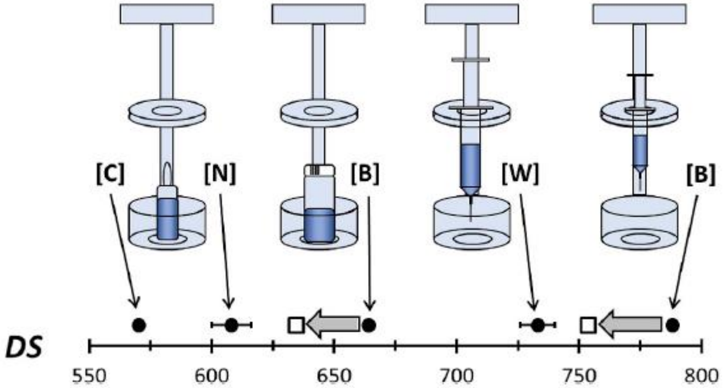
I used two PET nuclides as examples. The NIST primary standards were achieved with:

- 0.51 % combined standard uncertainty for Cu-64 activity
- 1.2 % combined standard uncertainty for I-124 activity

Dissemination of activity standards



I_γ



ARI 154, 108849 (2019).

NIST activity standards are the basis for:

- Benchmark radionuclide calibrator settings
- Revised absolute gamma-ray emission intensities
- Future calibrations

Original article

Nuclear Medicine Communications

An update on ‘dose calibrator’ settings for nuclides used in nuclear medicine

Denis E. Bergeron and Jeffrey T. Cessna

NMC 39, 500-504 (2018).

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- **Therapy**
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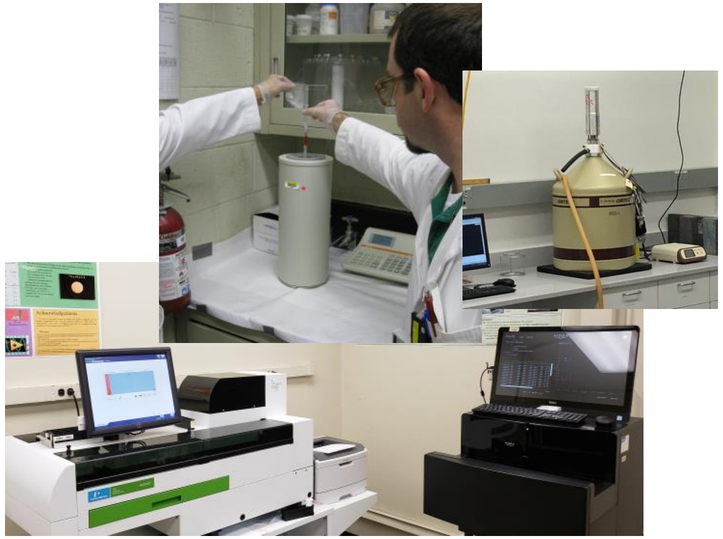
- **Dissemination**



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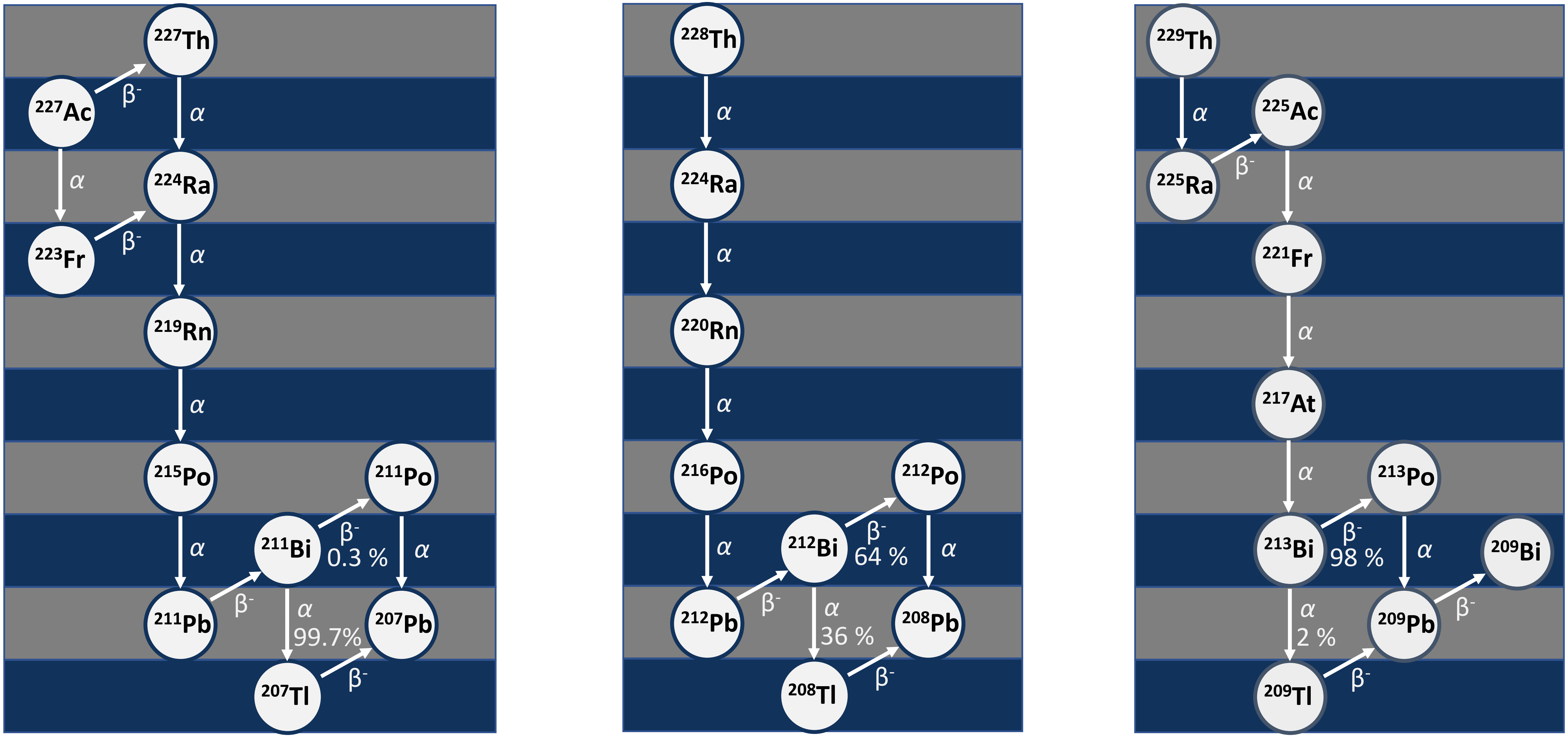
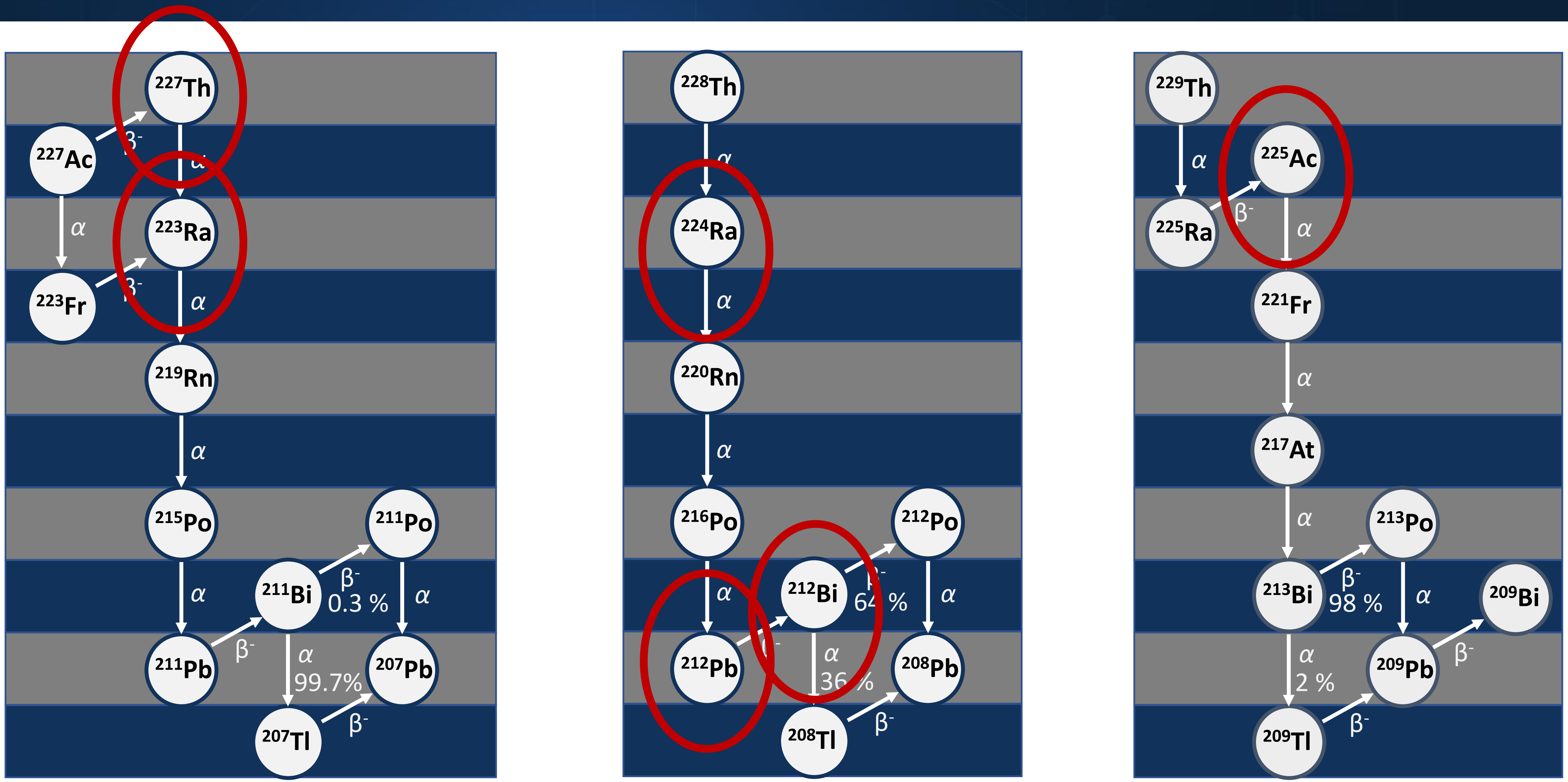
Alphas for therapy review

2012 2013 2014 2015 2016 2017 2018 2019 2020 2021 2022 2023

Medically important alpha emitters



(Some) Medically important alpha emitters



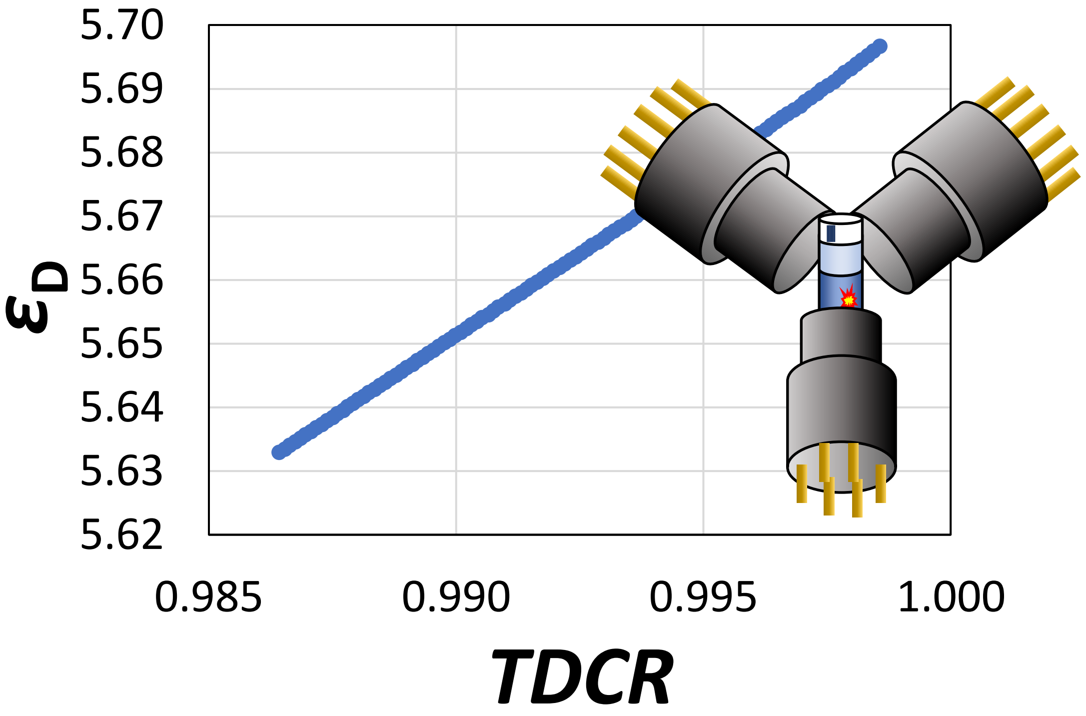
LS counting efficiencies from decay data

Triple-to-double Coincidence Ratio (TDCR) counting

$$TDCR = N_T/N_D = \varepsilon_T/\varepsilon_D$$

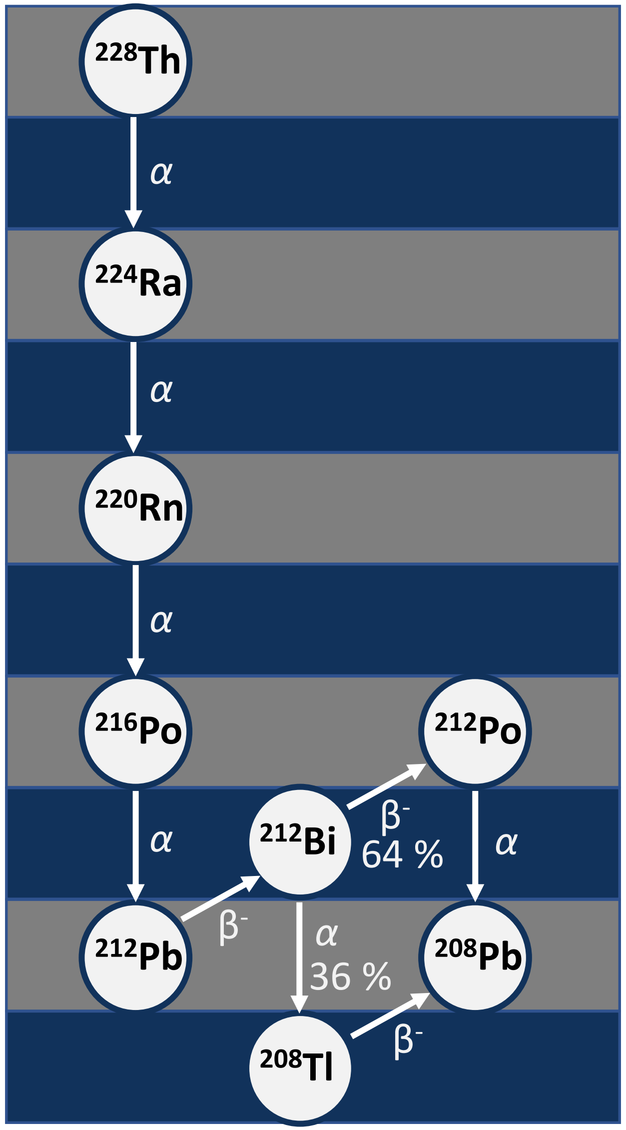
The MICELLE2 model* uses a Monte Carlo approach to calculate ε_T and ε_D for β^- decay branches

We got about 5.65 counts per ^{224}Ra decay



*Kossert & Grau Carles, Appl. Radiat. Isotop. 68, 1482-1488 (2010).

^{224}Ra decays by four α-emissions



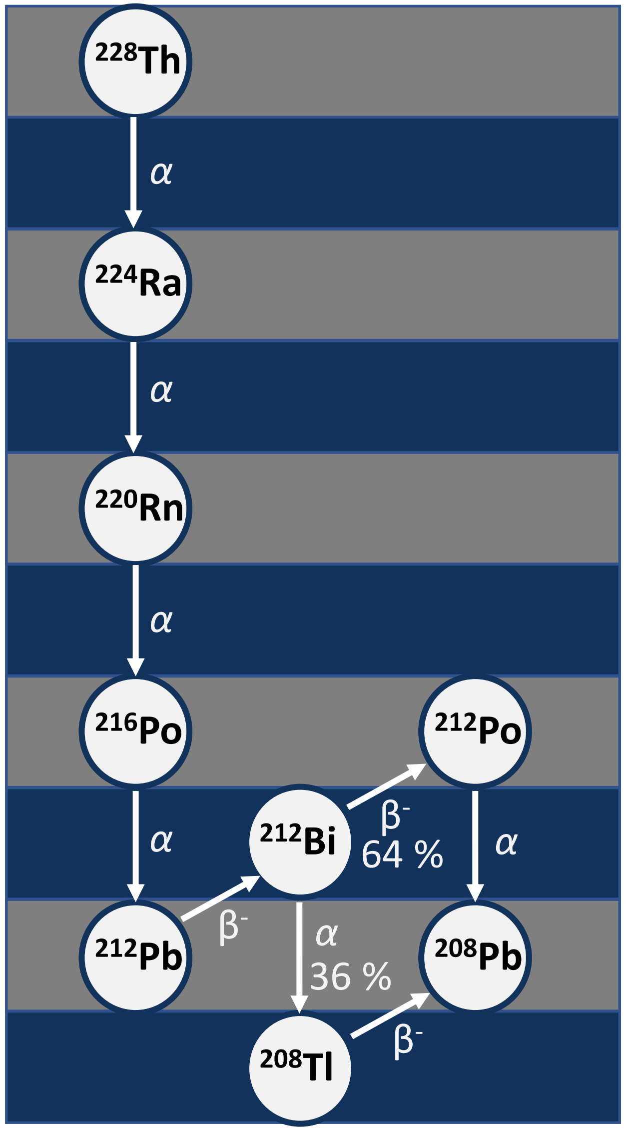
Following Bateman (1908), concentrations of isotopes in a decay chain are calculable from initial concentrations and decay constants (λ)

$$\frac{\mathrm{d}N_1}{dt} = -\lambda_1 N_1$$

$$\frac{\mathrm{d}N_i}{dt} = \lambda_{i-1} N_{i-1} - \lambda_i N_i \;\; (i = 2, n)$$

^{224}Ra reaches equilibrium >6 d after t_{sep}

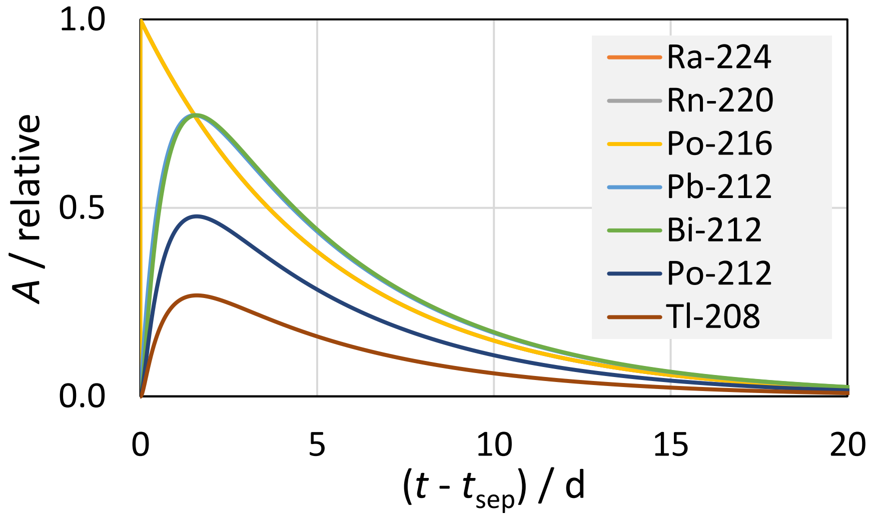
NIST

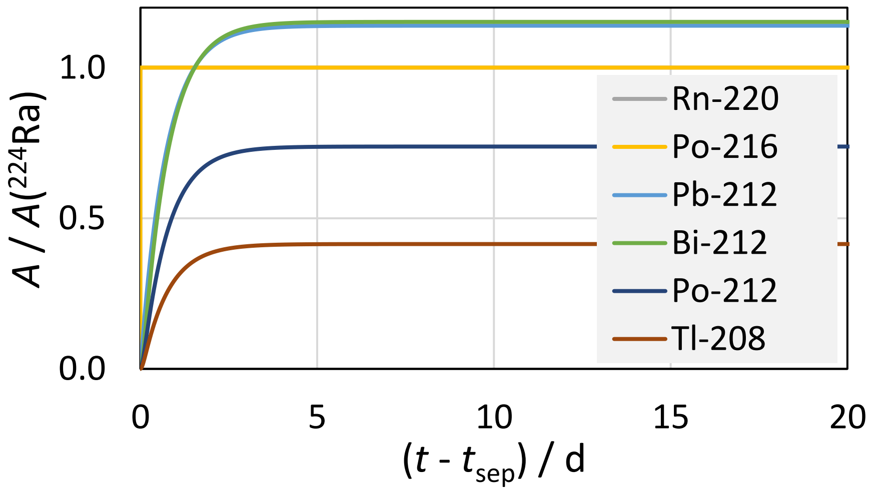


	$T_{1/2}$	$A/A_{Ra\text{-}224}$
^{224}Ra	3.631(2) d	1
^{220}Rn	55.8(3) s	1.000178(1)
^{216}Po	0.148(4) s	1.000178(1)
^{212}Pb	10.64(1) h	1.13928(15)
^{212}Bi	60.54(6) min	1.15263(15)
^{212}Po	300(2) ns	0.7385(11)
^{208}Tl	3.058(6) min	0.4144(20)

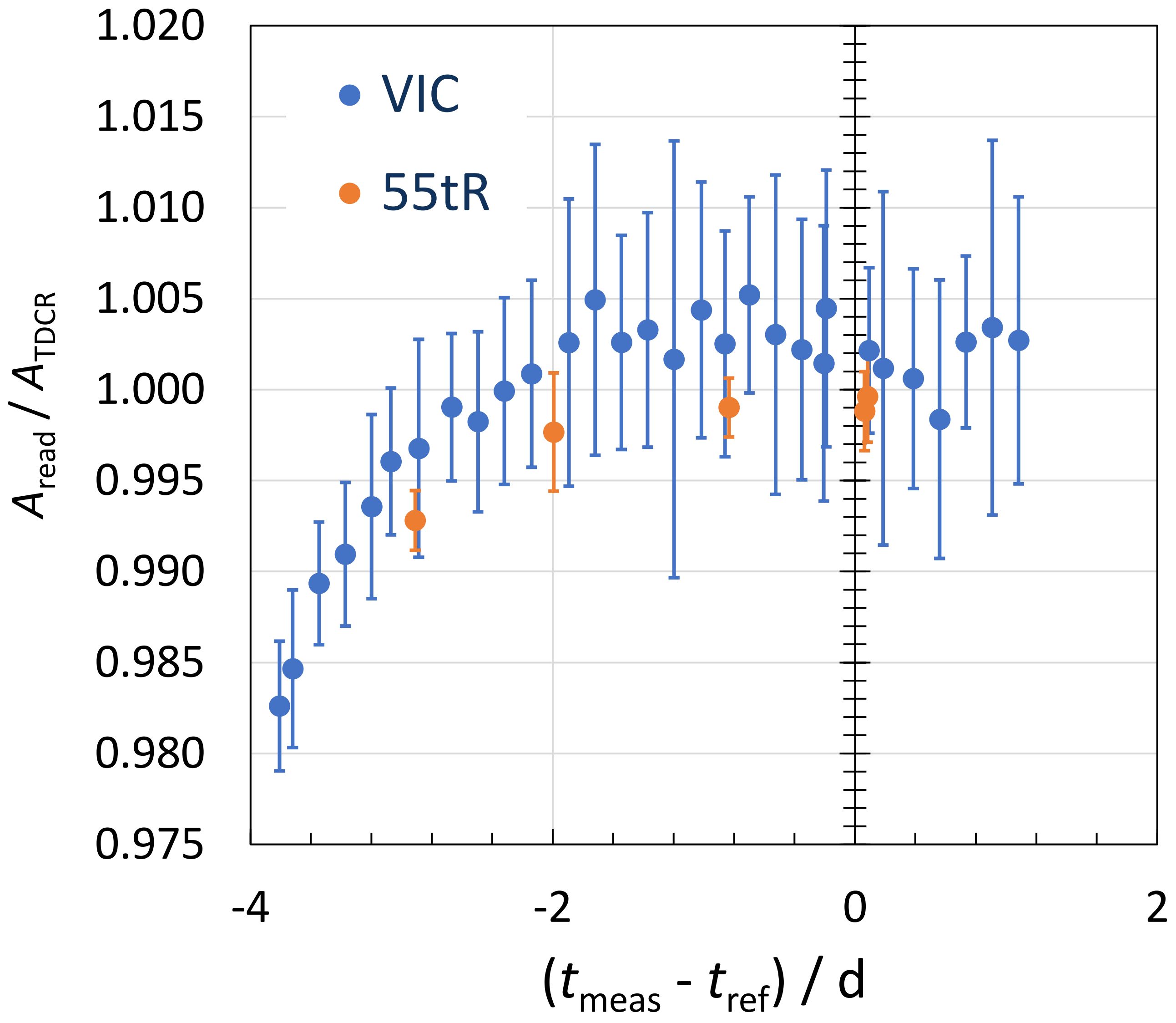
Most γ-rays in the decay chain come from ^{212}Pb and ^{208}Tl

Pre-equilibrium activity assays are tricky





Pre-equilibrium assay?

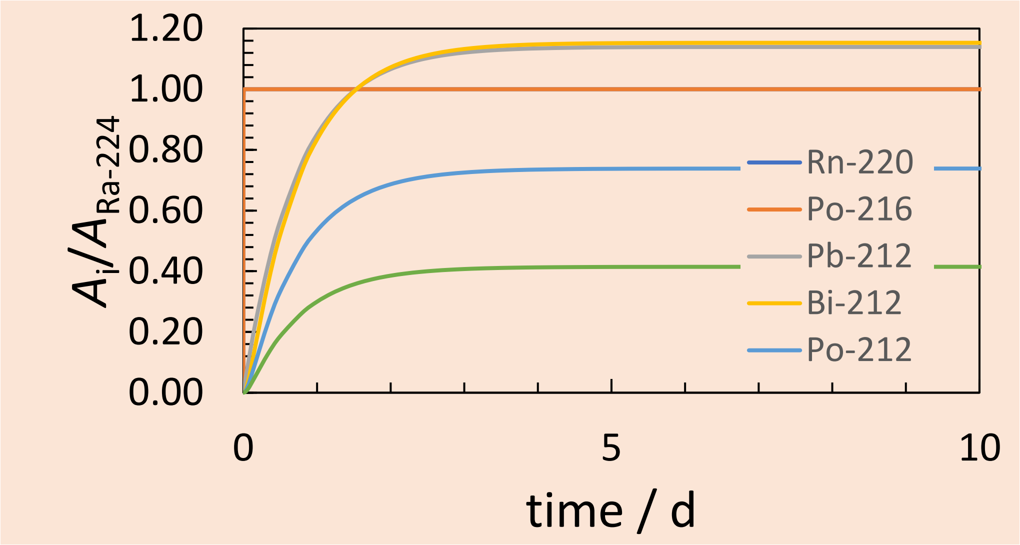


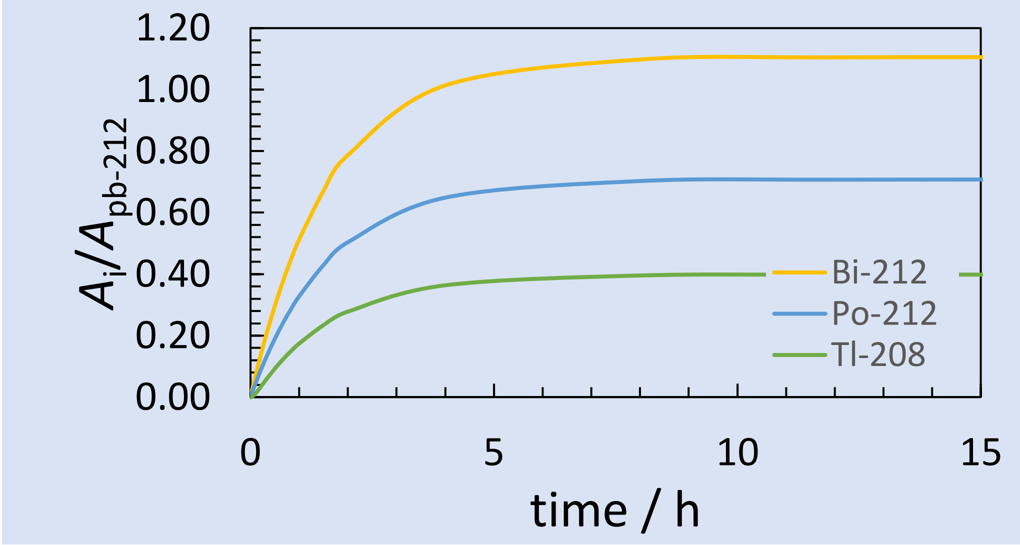
Most ionization chamber response is from progeny

Response changes rapidly during ingrowth

Pre-equilibrium assay requires good t_{sep}

Equilibration considerations





^{224}Ra (longest-lived progeny is ^{212}Pb, $T_{1/2}$ = 10.6 h) takes > 6 d to reach equilibrium

Separated from its parent, ^{212}Pb (longest-lived progeny is ^{212}Bi, $T_{1/2}$ = 60.55 min) reaches equilibrium in ~ 12 h.

Breakthrough of the parent leads to "supported" ^{212}Pb

Pb-212 radionuclide calibrator settings

NIST

^{207}Bi	Bismuth	846		1.7	38 Y	NBS73	Ref. for 1064, 569.7, 76.7, 1772 keV
^{208}Tl	Thallium	571÷2			3.07 M	NM75	
^{212}Pb	Lead	101			10.6 H	NM75	Decays to ^{212}Bi; eqb. after 1 hr. See App. II.
^{212}Bi	Bismuth	489×10			60.5 M	NM75	
^{212}Pb (Eqb. ^{212}Bi)	Lead	158					Eqb. after 8 hrs. Reading gives Act. of Pb in eqb. sample.
^{212}Bi (Eqb. ^{212}Pb)	Bismuth	135					Reading gives Act. of Bi in eqb. sample.
^{212}Pb / ^{212}Bi Eqb.	Lead, / Bismuth	030 or 146×2					Reading gives Total Act. of Pb & Bi in eqb. sample.
^{224}Ra	Radium	646×100			3.64 D	NM75	
^{226}Ra	Radium	778		0.5	1622 Y	NBS73	Reading in grams. Com-

Capintec Inc, 1986. Radionuclide Calibrator Owner's Manual, Revision E. Ramsey. Capintec Inc, NJ.

Pb-212 radionuclide calibrator settings

^{207}Bi	Bismuth	846	1.7	38 Y	NBS73	Ref. for 1064, 569.7, 76.7,
^{208}Tl	Thallium	571÷2				
^{212}Pb	Lead	101				
^{212}Bi	Bismuth	489×10				
^{212}Pb	Lead (Eqb. ^{212}Bi)	158				
^{212}Bi	Bismuth (Eqb. ^{212}Pb)	135				eqb. sample.
^{212}Pb / ^{212}Bi (Eqb.)	Lead, Bismuth	030 or 146×2				Reading gives Total Act. of Pb & Bi in eqb. sample.
^{224}Ra	Radium	646×100		3.64 D	NM75	
^{226}Ra	Radium	778	0.5	1622 Y	NBS73	Reading in grams. Com-

nuclide in isolation and as m2 when in equilibri

IC model	^{212}Pb			
	DS	u_c/%	u_A/%	m
CRC-55tR	662	5.7	3.4	10
CRC-25R	662	5.7	3.4	

Napoli et al., ARI 166, 109362 (2020).

Capintec Inc, 1986. Radionuclide Calibrator Owner's Manual, Revision E. Ramsey. Capintec Inc, NJ.

Pb-212 radionuclide calibrator settings

NIST

Seems Capintec settings neglect progeny beyond ^{212}Bi

The 2.6 MeV γ-ray from ^{208}Tl accounts for much of the overall ionization chamber response to ^{212}Pb and its progeny

For decay chain nuclides especially, users should take care when referencing theoretically-determined radionuclide calibrator settings

nuclide in isolation and as m2 when in equilibriu

IC model	^{212}Pb			
	DS	u_c/%	u_A/%	m
CRC-55tR	662	5.7	3.4	10
CRC-25R	662	5.7	3.4	

Napoli et al., ARI 166, 109362 (2020).

<u>Settings result in 3x to 8x errors.</u>

Capintec Inc, 1986. Radionuclide Calibrator Owner's Manual, Revision E. Ramsey. Capintec Inc, NJ.

Plenty to consider with alpha emitters

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Review

Realization and dissemination of activity standards for medically important alpha-emitting radionuclides

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A R T I C L E I N F O

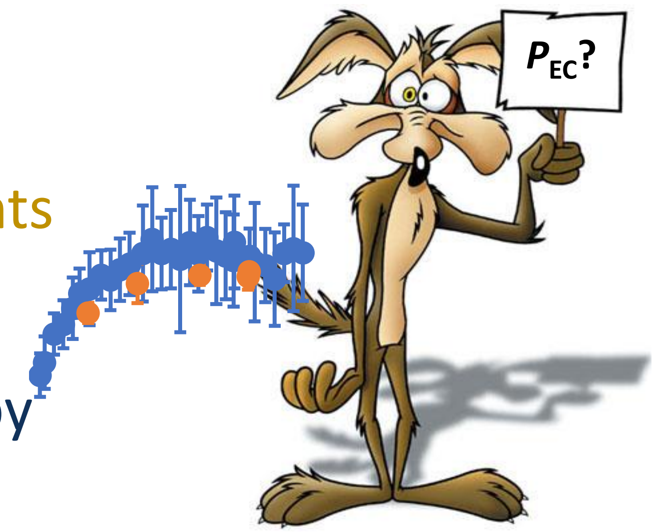
Keywords:
Liquid scintillation counting
Coincidence counting
Gamma-ray spectrometry
Ra-223
Ra-224
Ac-225
Th-227
Decay chain
Activity calibration
HPGe
Dose calibrator

A B S T R A C T

Interest in targeted cancer therapy with alpha-emitting radionuclides is growing. To evaluate emerging radiotherapeutic agents requires precise activity measurements for consistent dose-response relationships and patient-specific dosimetry. National metrology institutes around the world have reported on the development and comparison of activity standards for medically important alpha emitters. This review describes the relevant methods and models underpinning these standards, the generation of new nuclear decay data, and the impacts on preclinical and clinical activity assays using radionuclide calibrators and γ-ray spectrometry.

Summary

- **Challenges with medical nuclides**
  - EC branches and decay data uncertainties
  - Decay chain nuclides and pre-equilibrium measurements
- **Demand for standards is high**
  - Era of theranostics and targeted molecular radiotherapy
  - <u>We are hiring</u>



^{177}Lu comparison
^{133}Ba phantoms
^{18}F standard
^{68}Ge phantom
^{123}I dose cal factors
^{68}Ge mock syringe update
^{223}Ra standard & data
^{133}Ba calibrator misuse
^{64}Cu standard & data
^{64}Cu & ^{18}F SIRTI comparison
Dose cal review
^{68}Ge comparison & data
^{124}I standard
^{224}Ra standard & data
^{90}Y branching
^{124}I data
^{224}Ra comparison
^{212}Pb standard & data
Alphas for therapy review

2012 2013 2014 2015 2016 2017 2018 2019 2020 2021 2022 2023

NIST Nuclear Medicine Project Team

Brian E. Zimmerman (lead), Jeffrey T. Cessna
Ryan Fitzgerald, Leticia Pibida, Lizbeth Laureano-Pérez, Ron Collé

Questions about our research or postdoc opportunities?

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