IN SEARCH OF EXOTIC EVENTS FOR PET: A GAMMASPHERE EXPERIMENT

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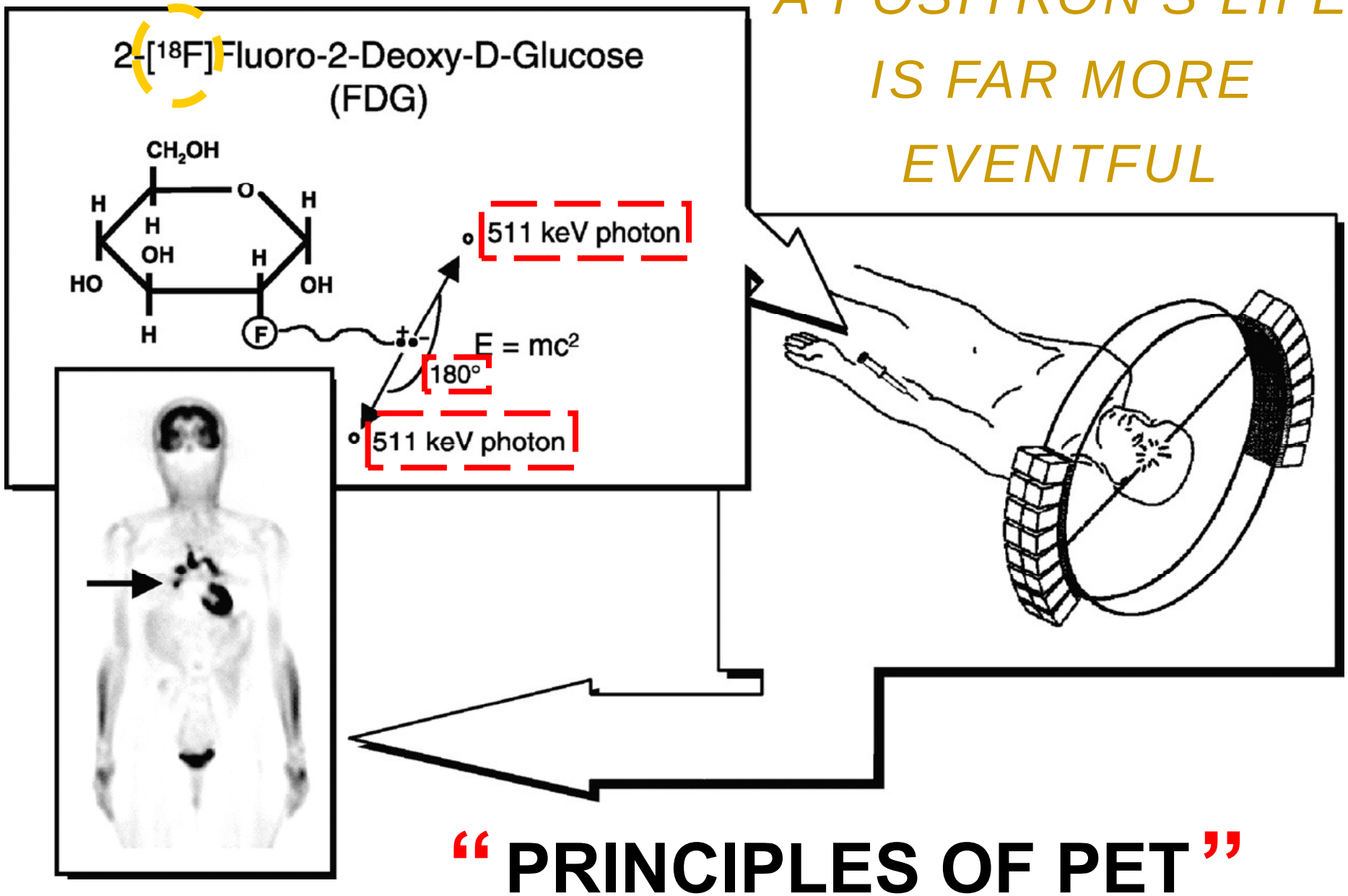
UNIVERSITY OF SURREY

e^+ EMITTER: CLINICAL SOURCE

A POSITRON'S LIFE IS FAR MORE EVENTFUL

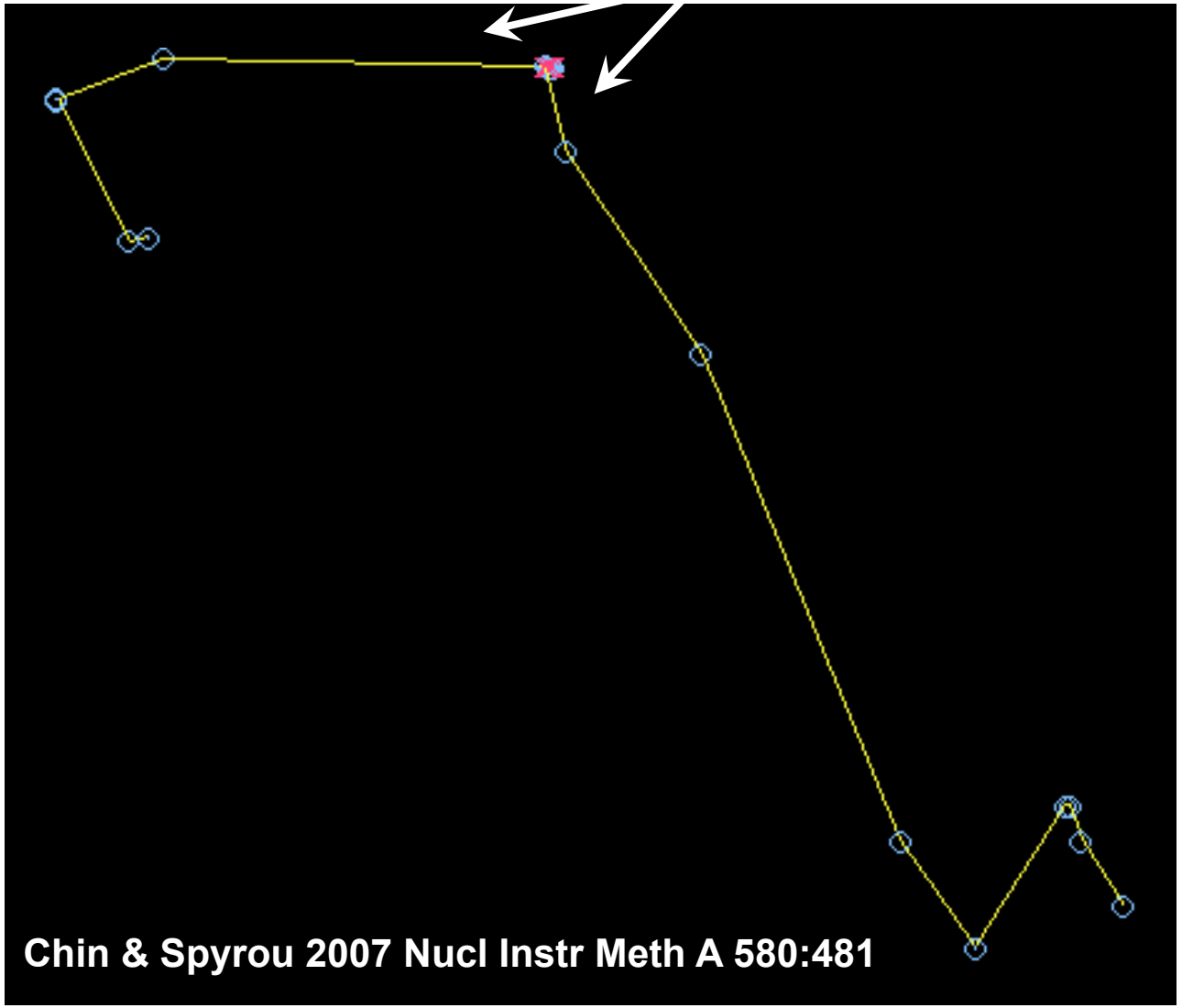


"PRINCIPLES OF PET"

REPRODUCED FROM PHELPS ME ANN. REV. NUCL. PART. SCI. 2002;52:303-38

Positron about to decay in flight	1	0.606	1	2	0.155,0.023,500.314	-0.122.-0.592. 0.797
Resulting photons	1	0.979	0	2	0.155,0.023 500.314	-0.311, 0.020, 0.950
	2	0.649	0	2	0.155,0.023 500.314	0.282,-0.935,-0.213

NOT 0.511 *NOT BACK-TO-BACK!*



IN SEARCH OF EXOTIC EVENTS FOR PET: A GAMMASPHERE EXPERIMENT

PREVIOUS WORK (previous slide)

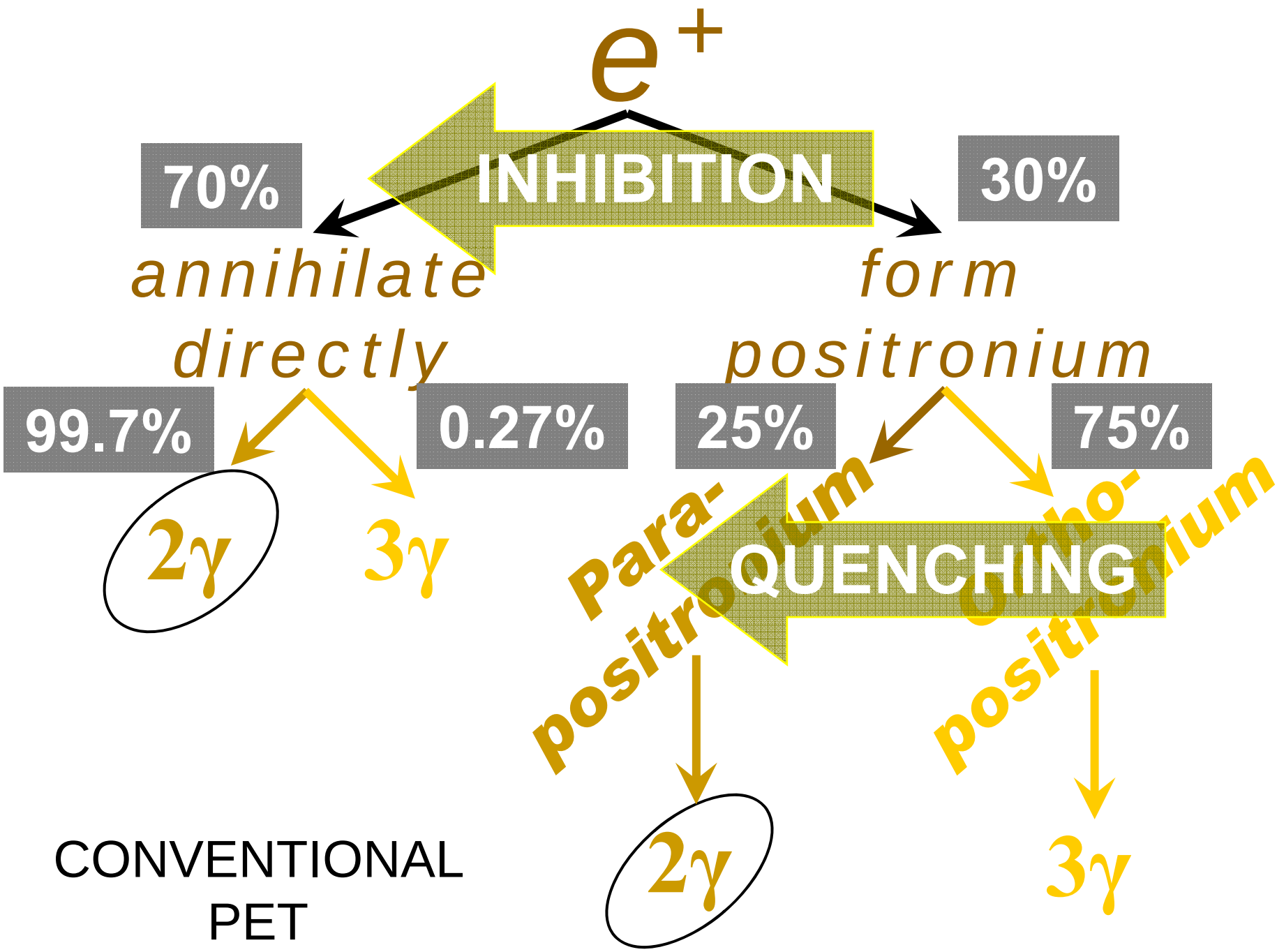
NOT 511 keV & NOT BACK-TO-BACK

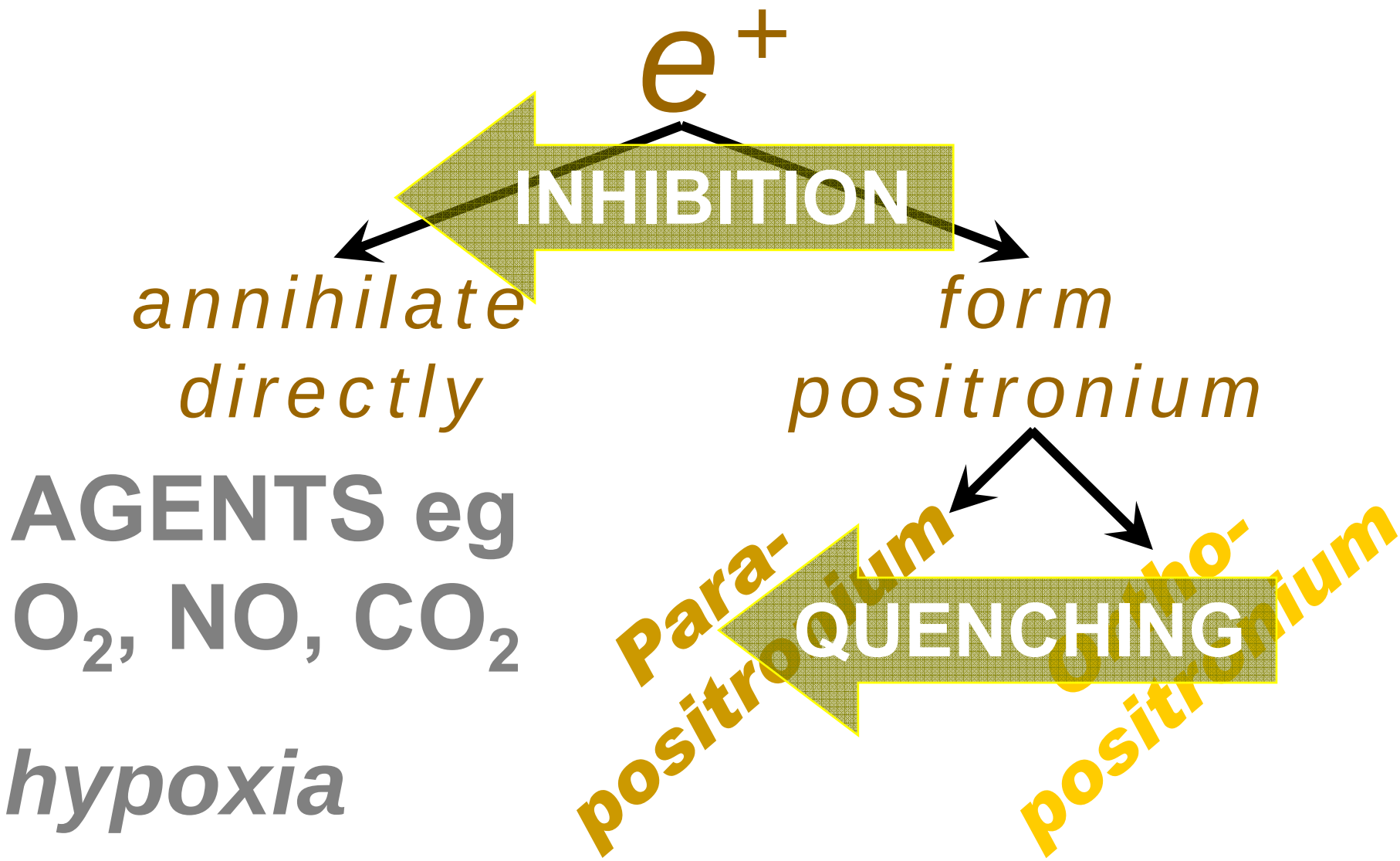
Monte Carlo

THIS WORK

NOT TWO BUT THREE PHOTONS

Real !


e+
INHIBITION
70%
30%
annihilate directly
form positronium
99.7%
0.27%
25%
75%
2γ
3γ
Para-positronium
Ortho-positronium
QUENCHING
2γ
3γ
CONVENTIONAL PET



PROSPECTS FOR MOLECULAR IMAGING

MEASURE $3\gamma/2\gamma$ *YIELD*

FIND OUT O_2 *IN BODY TISSUES?*

PROSPECTS FOR MOLECULAR IMAGING

IEEE TRANSACTIONS ON MEDICAL IMAGING, VOL. 23, NO. 4, APRIL2004

PROPOSAL

Three-Gamma Annihilation Imaging in Positron Emission Tomography

Krzysztof Kacperski*, Nicholas M. Spyrou, and F. Alan Smith

Abstract—**It is argued that positron annihilation into three photons, although quite rare, could still be used as a new imaging modality of positron emission tomography. The information gained when the three decay photons are detected is significantly higher than in the case of 511 keV two-gamma annihilation. The performance of three-gamma imaging in terms of the required detector properties, spatial resolution and counting rates is discussed. A simple proof-of-principle experiment confirms the feasibility of the new imaging method.**

Index Terms—**Positron emission tomography, three-gamma annihilation.**

5. Conclusions

REFUTAL

Three-gamma imaging is potentially more powerful than standard PET because each event bears the complete position information enabling the localization of the activity distribution without use of back-projection tomographic techniques. However, only a subfraction of the three-photon events are usable as each photon energy must be above the detection threshold and only total energy deposition events can used, as a tight total energy window and time window (<5 ns) must be applied (for typical source strengths used in imaging) to reduce the strong background from two-photon decay pile-up events. However, these conditions can be met with high-resolution semiconductor detectors as pointed out in Kacperski and Spyrou (2005), and construction of a detection system with the required attributes for such studies is not beyond the reach of current technology.

The present work answers one question raised by Kacperski and Spyrou (2005) concerning the potential biological sensitivity of the three-photon imaging. Unfortunately, one should not expect any sensitivity to the level of dissolved O_2. Our results indicate that the overall three-photon yield is about 0.5% in all samples. These conclusions assume that the direct three-photon yield is identical to that for free e^-s. Only direct measurement of the three-photon yield can determine if this assumption is correct (Seweryniak 2006).

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Table 1. The delayed (F_3^{de}) and total (F_3) three-photon yields as well as the fit parameters (K_p and K_{cap}/λ_d) for the various liquid samples (HSA is for human serum albumin).

Material	Oxygen	F_3^{de} (%)	F_3 (%)	K_p (ns^{-1})	$R = K_{cap}/\lambda_d$
Iso-octane	Low	0.58	0.85	1.34	2.15
	High	0.39	0.65	2.27	2.06
Water	Low	0.26	0.52	2.77	3.05
	High	0.25	0.51	2.84	3.07
Saline	Low	0.24	0.51	2.86	3.14
	High	0.24	0.51	2.98	3.07
HSA	Low	0.25	0.51	2.64	3.30
	High	0.25	0.51	2.95	2.96
Blood	Venous	0.25	0.52	2.86	3.02

The present work answers one question raised by Kacperski and Spyrou (2005) concerning the potential biological sensitivity of the three-photon imaging. Unfortunately, one should not expect any sensitivity to the level of dissolved O_2. Our results indicate that the overall three-photon yield is about 0.5% in all samples. These conclusions assume that the direct three-photon yield is identical to that for free e^-s. Only direct measurement of the three-photon yield can determine if this assumption is correct (Seweryniak 2006).

REPRODUCED FROM MERCURIO K et al PHYS. MED. BIOL. 2006;51:N323-9

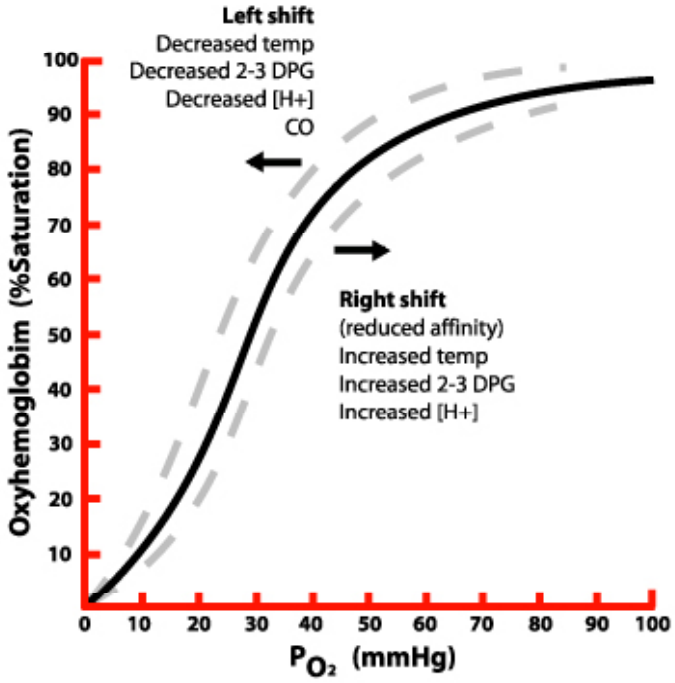
MEASURE 3γ/2γ YIELD

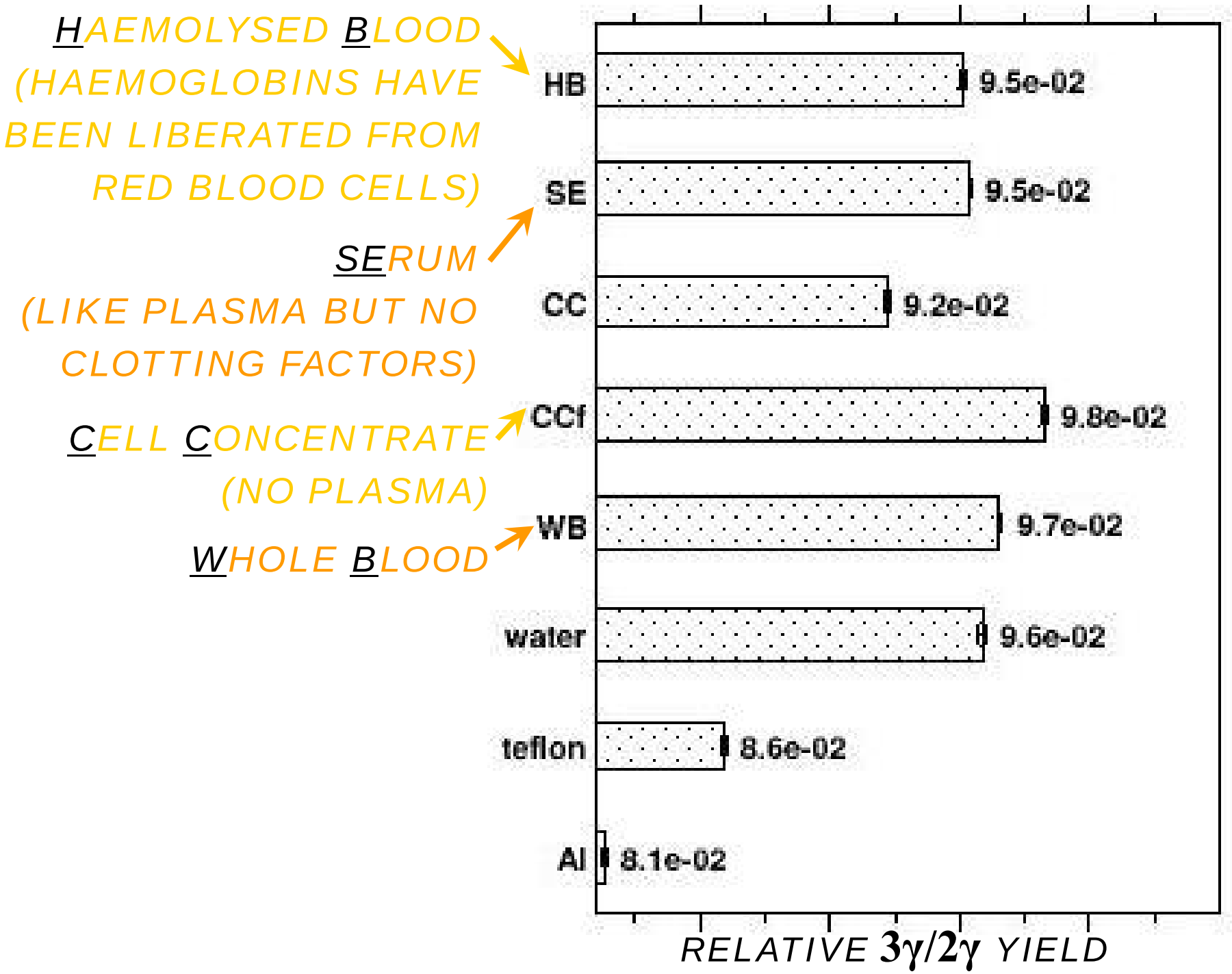
?

FIND OUT O_2 IN BODY TISSUES?

WHAT DO WE MEAN?

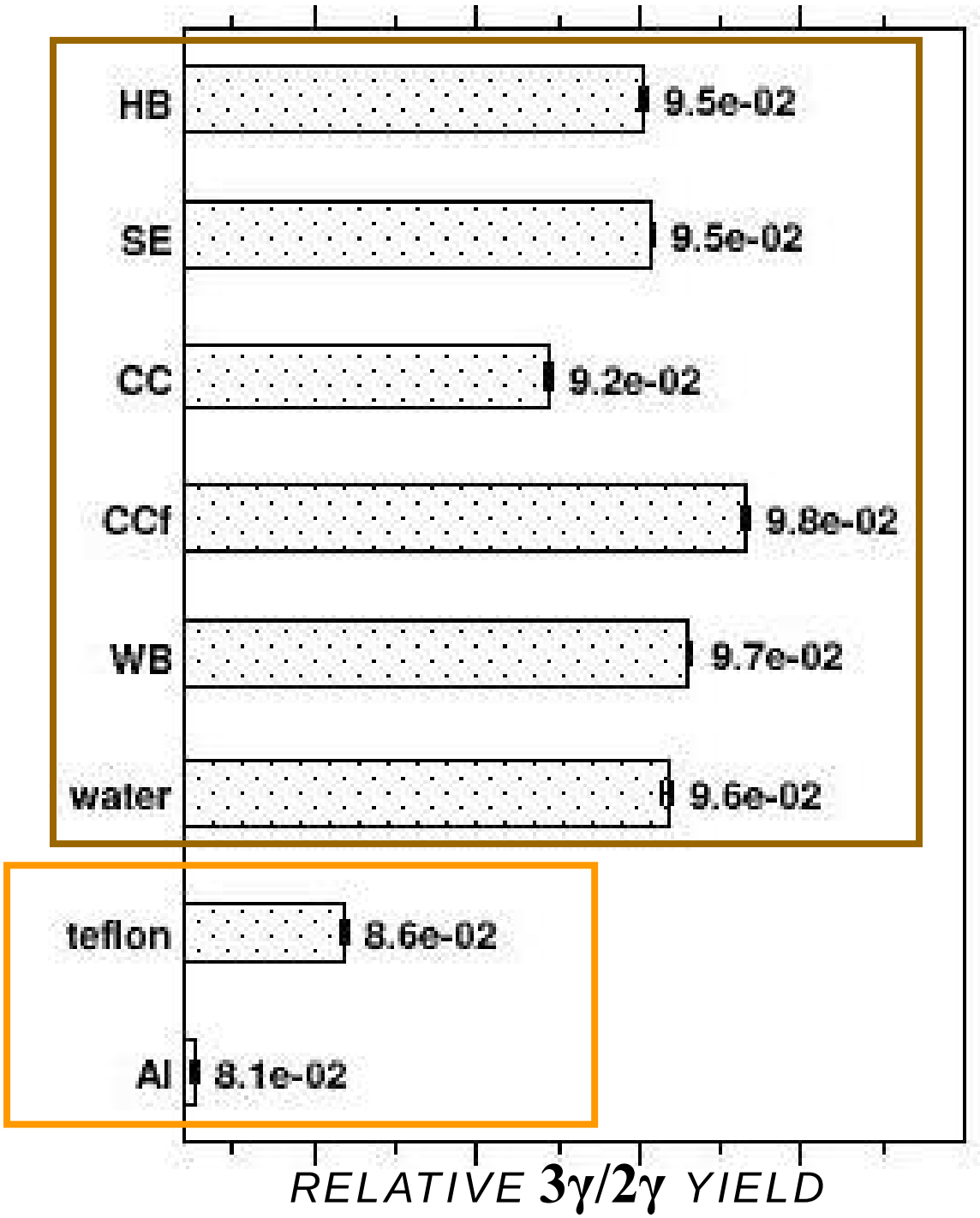
LOOSE OR BOUND?




HAEMOLYSED BLOOD
(HAEMOGLOBINS HAVE
BEEN LIBERATED FROM
RED BLOOD CELLS)
SERUM
(LIKE PLASMA BUT NO
CLOTTING FACTORS)
CELL CONCENTRATE
(NO PLASMA)
WHOLE BLOOD
HB
SE
CC
CCf
WB
water
teflon
Al
9.5e-02
9.5e-02
9.2e-02
9.8e-02
9.7e-02
9.6e-02
8.6e-02
8.1e-02
RELATIVE 3γ/2γ YIELD

THE FACT THAT THEY VARY IS ENCOURAGING – AT LEAST THE METHOD IS SENSITIVE TO *SOMETHING*

CONFIRMS VALUES IN THE LITERATURE

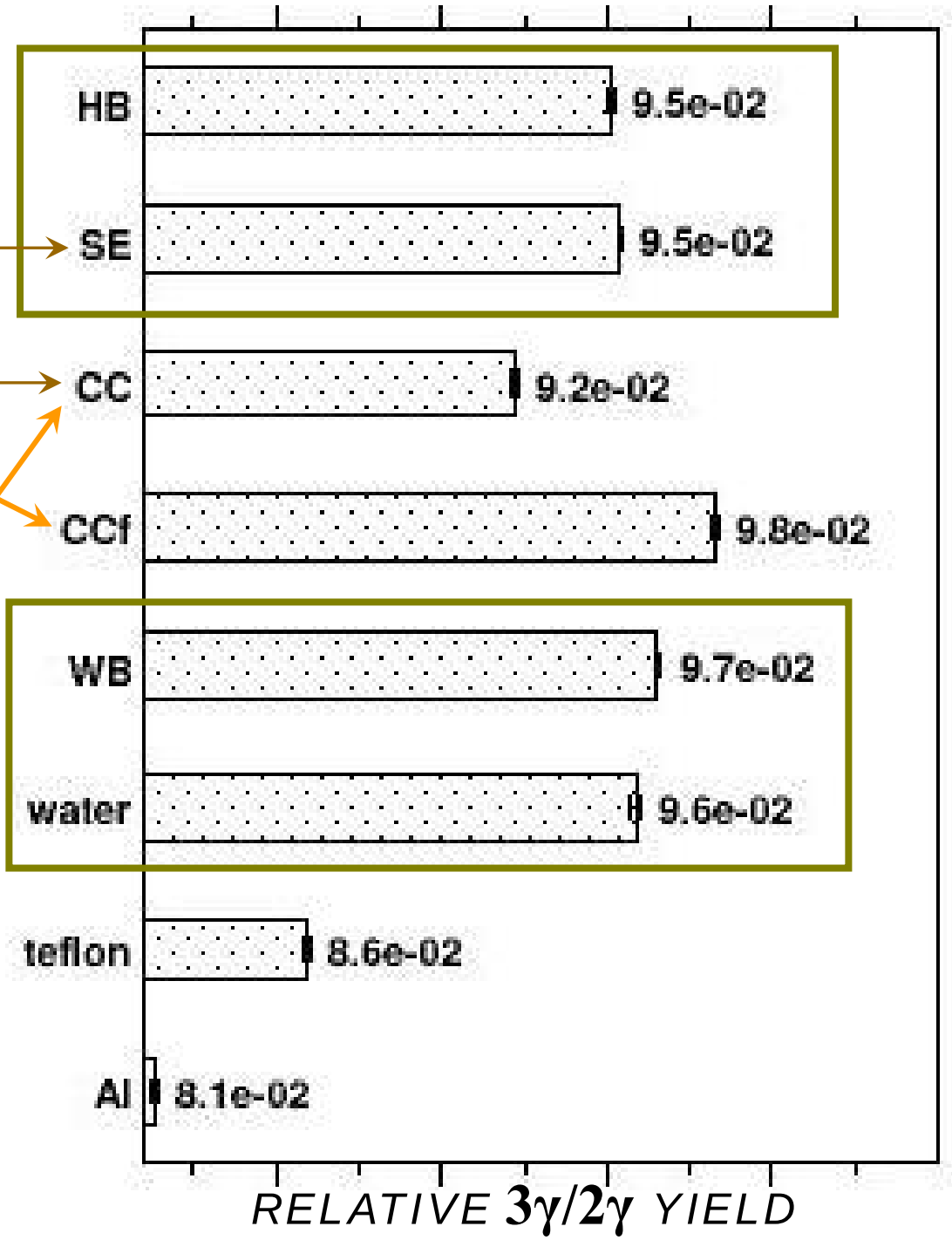


MOST WATER-LIKE

LEAST WATER-LIKE

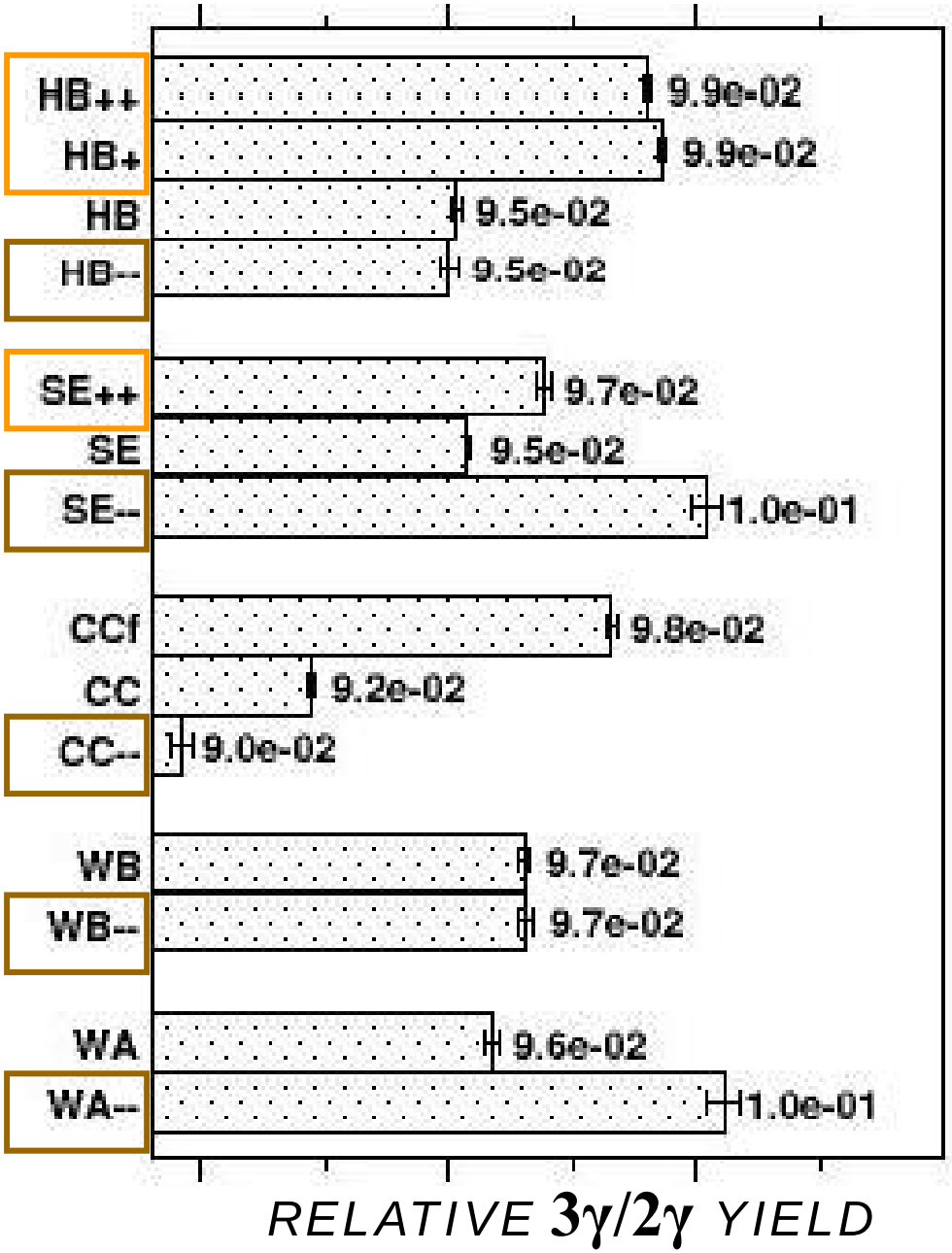
CAN DIFFERENTIATE 'LIFE'!

CAN'T EXPECT THESE TO VARY VERY MUCH COZ THEY ARE EXPOSED TO THE ATMOSPHERE



OXYGENATED

DEOXYGENATED



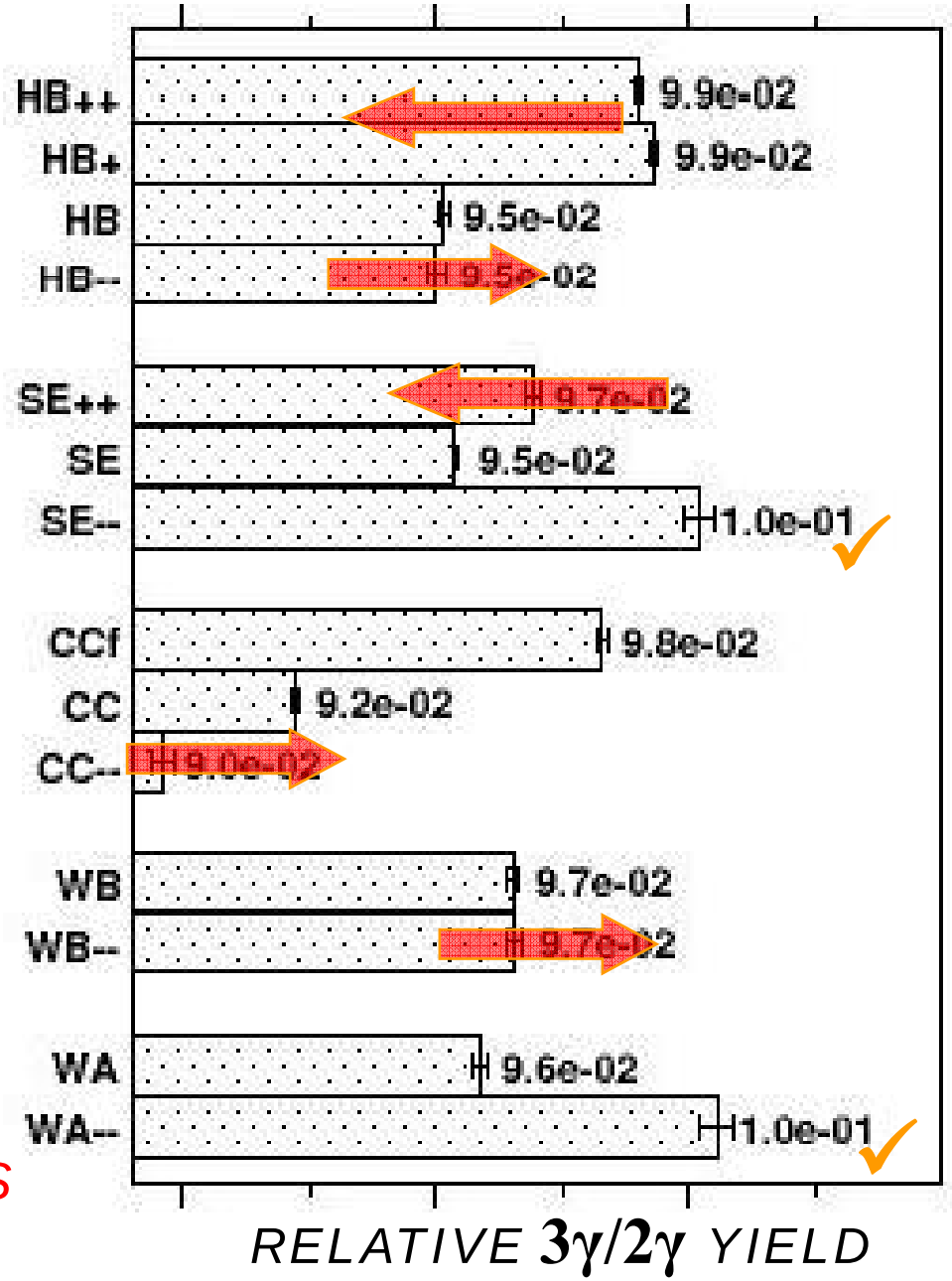
IF O_2 WERE THE ONLY FACTOR

EXPECTED

O_2↓ YIELD↑

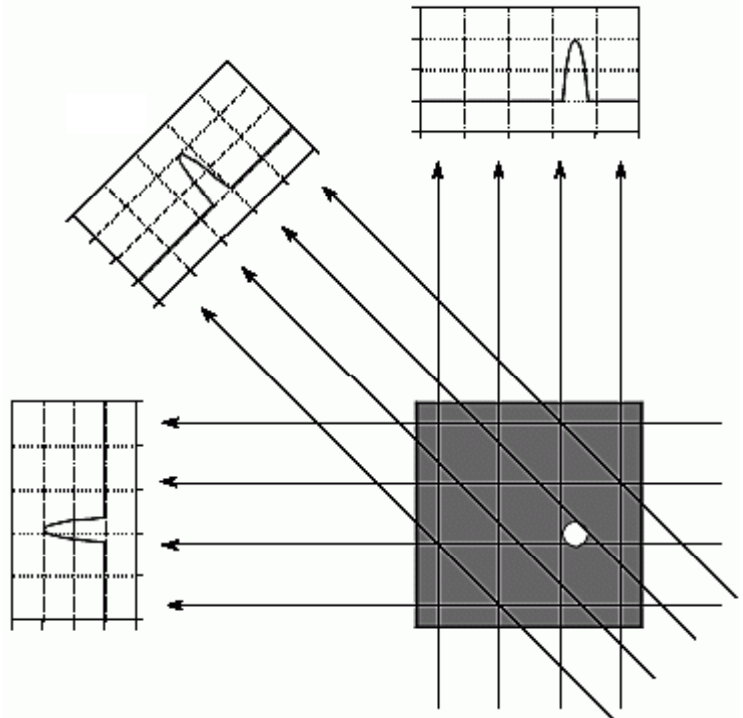
UNEXPECTED

CONFOUNDING FACTORS



2γ PET

IMAGE RECONSTRUCTION



WE HAVE TO BACK-PROJECT COZ WE DON'T KNOW AT WHICH POINT THE ANNIHILATION HAPPENED

LINE OF RESPONSE

3γ PET

Local chemistry ✓

By conservations of energy & momentum

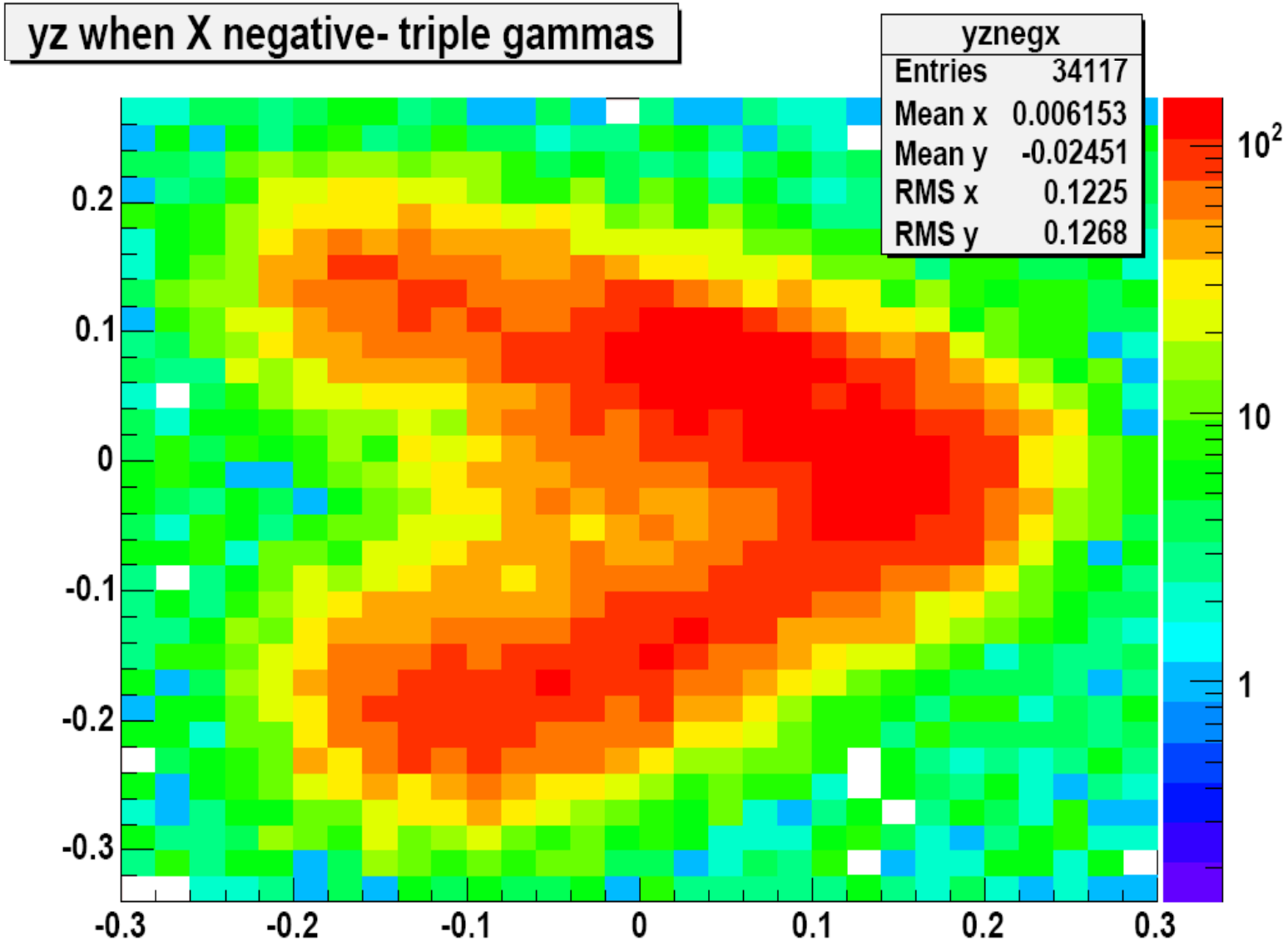
KNOWN	UNKNOWNS
(E_1, α_1)	(x_1, y_1, z_1)
(E_2, α_2)	
(E_3, α_3)	

solve simultaneous eqs

POINT OF RESPONSE

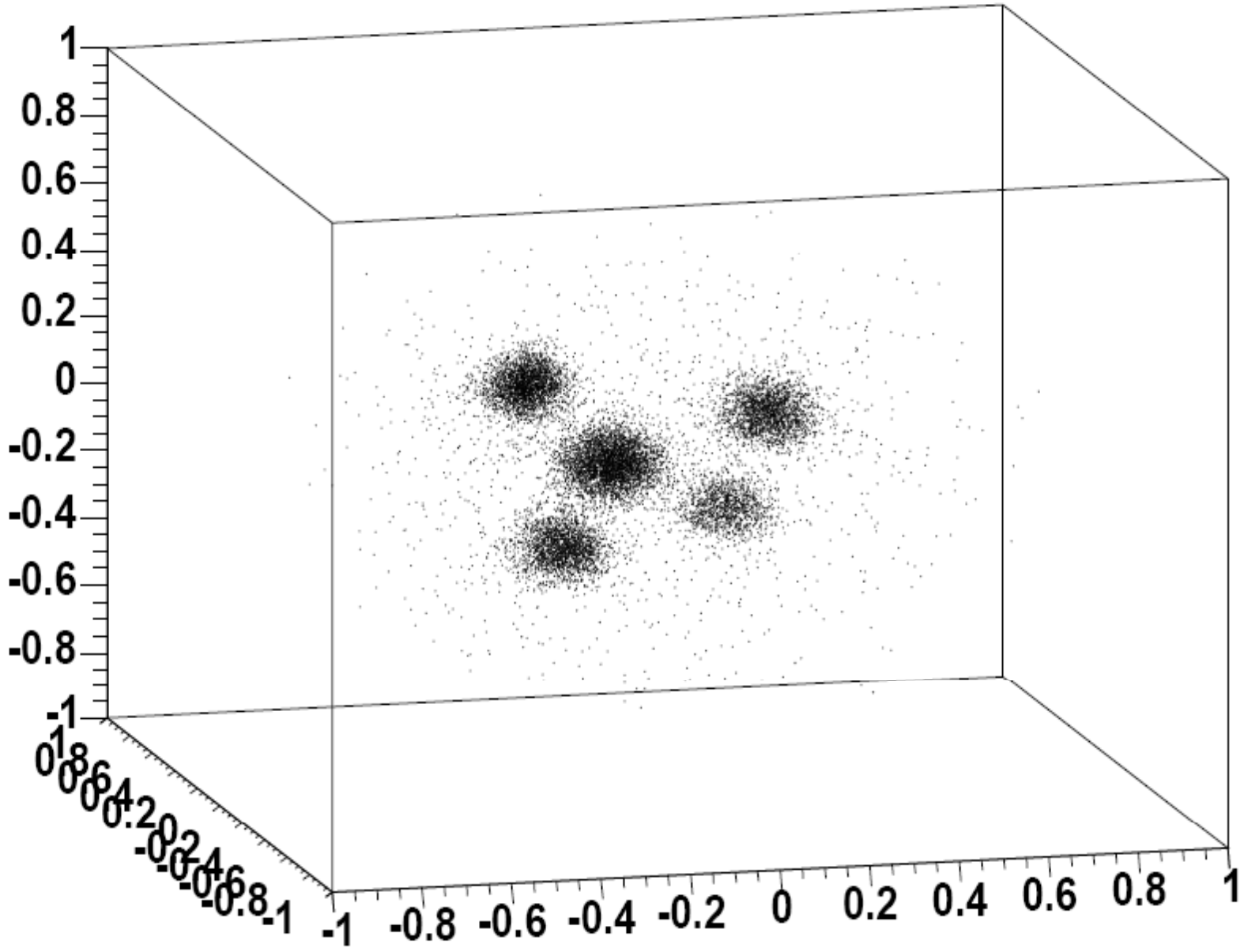
Argonne NATIONAL LABORATORY

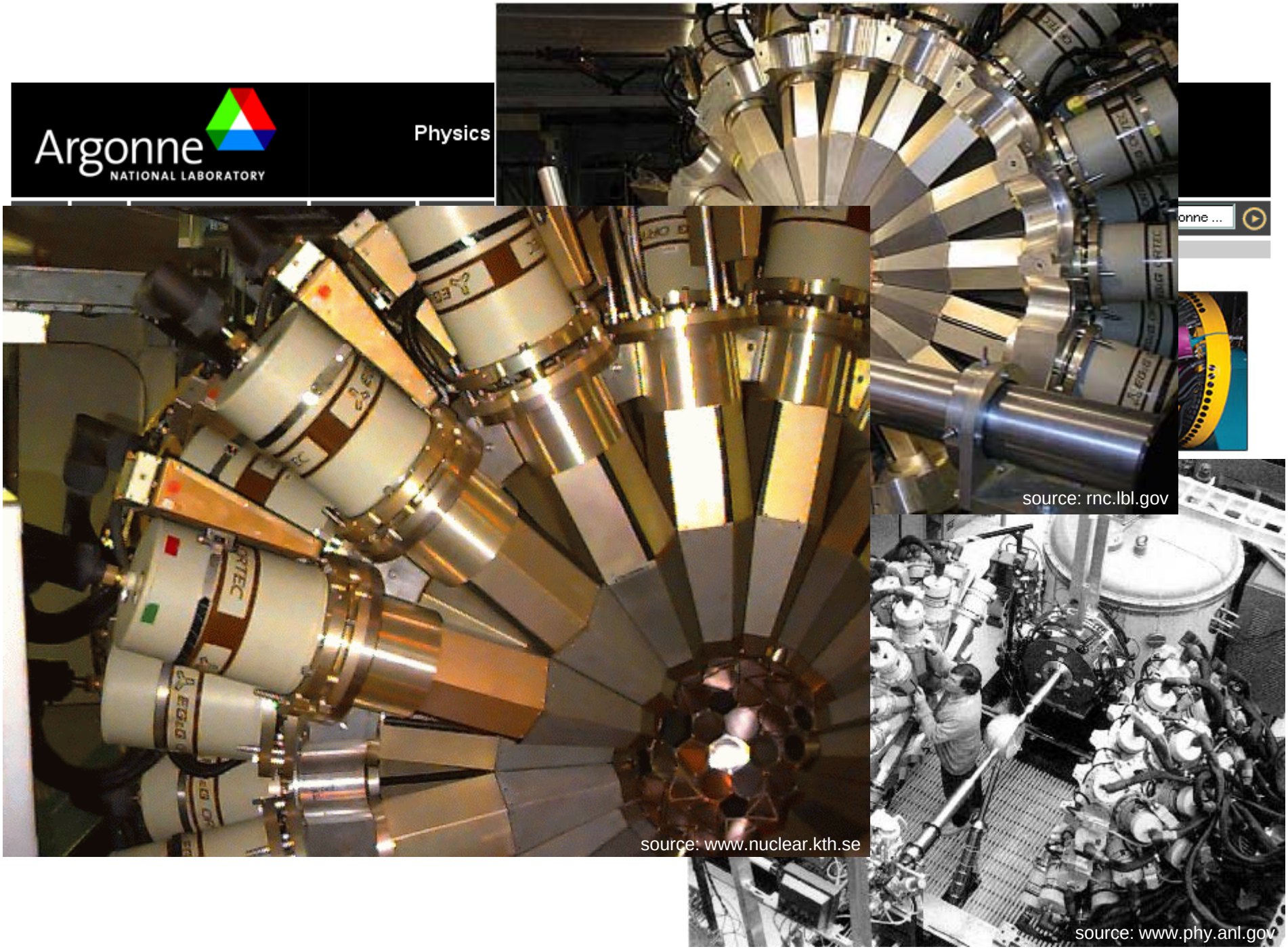
LOGO PAINTED WITH BLOOD ON STYROFOAM CUBE



x, y, z for triple events

5 SOURCES INSIDE
STYROFOAM CUBE




Argonne
NATIONAL LABORATORY
Physics
source: rnc.lbl.gov
source: www.nuclear.kth.se
source: www.phy.anl.gov

GAMMASPHERE: AN UNPRECEDENTED LUXURY FOR US

LUXURY #1 NEAR-4π SOLID ANGLE

LUXURY #2 MULTI-DIMENSIONAL DATA WRITTEN OUT

```
BIT - EVENT PROCESSING CONTROL BITS

 1  gcmode          gain correction on/off
 2  tmmode          time veto on/off
 3  hmode           adjacent detector veto on/off

BIT - EVENT DATA CONTROL BITS FOR EACH DETECTOR

 4  writeget        output ge time on/off
 5  writegef        output full ge data on/off
 6  writebgo        output of BGO data on/off

BIT - EVENT DATA CONROL BITS FOR EACH EVENT

 7  writeallge      output of dirty ge data on/off
 8  writeallbgo     output of clean bgo data on/off

BIT - MISC

 9  writeIsomerTag
10  rf_timing       ge times calculated vs rf pulses
                    (subtract tac2 on the fly)
```

GAMMASPHERE: AN UNPRECEDENTED LUXURY FOR US

LUXURY #1 NEAR-4π SOLID ANGLE

```
1 hpid          bgo hit pattern     (0xfe00) |1111|1110|0000|0000| [1]
                and ge hit bit      (0x0100) |0000|0001|0000|0000|
                and id register     (0x00ff) |0000|0000|1111|1111|
2 ge_high       14 bit high res ge  (0x3fff) |0011|1111|1111|1111|
                and over-range bit  (0x4000) |0100|0000|0000|0000|
                and Pileup bit      (0x8000) |1000|0000|0000|0000|
3 ge_side       12 bit side ch ge   (0x0fff) |0000|1111|1111|1111| [2]
```

The appropriate mask to extract the information is shown both in hex and binary formats.

The rest of the events depend on what EFF write out options are on:

If the "writeget" [4] (germanium time) or "writegef" [5] (trap + lowres signals) are set

```
4 ge_time 12/13 bit[5] ge time  (0x1fff) |0001|1111|1111|1111|
```

If "writegef" [5] (trap + lowres signals) is set:

```
5 ge_trap       12 bit trap corr    (0x0fff) |0000|1111|1111|1111|
6 ge_low        12 bit low res ge   (0x0fff) |0000|1111|1111|1111|
```

If "writebgo" [6] (clean bgo) is set:

```
7 bgo_time      12 bit bgo time     (0x0fff) |0000|1111|1111|1111| [3]
8 bgo_low       12 bit bgo energy   (0x0fff) |0000|1111|1111|1111| [3]
```

DARK LINES
A few detectors not working

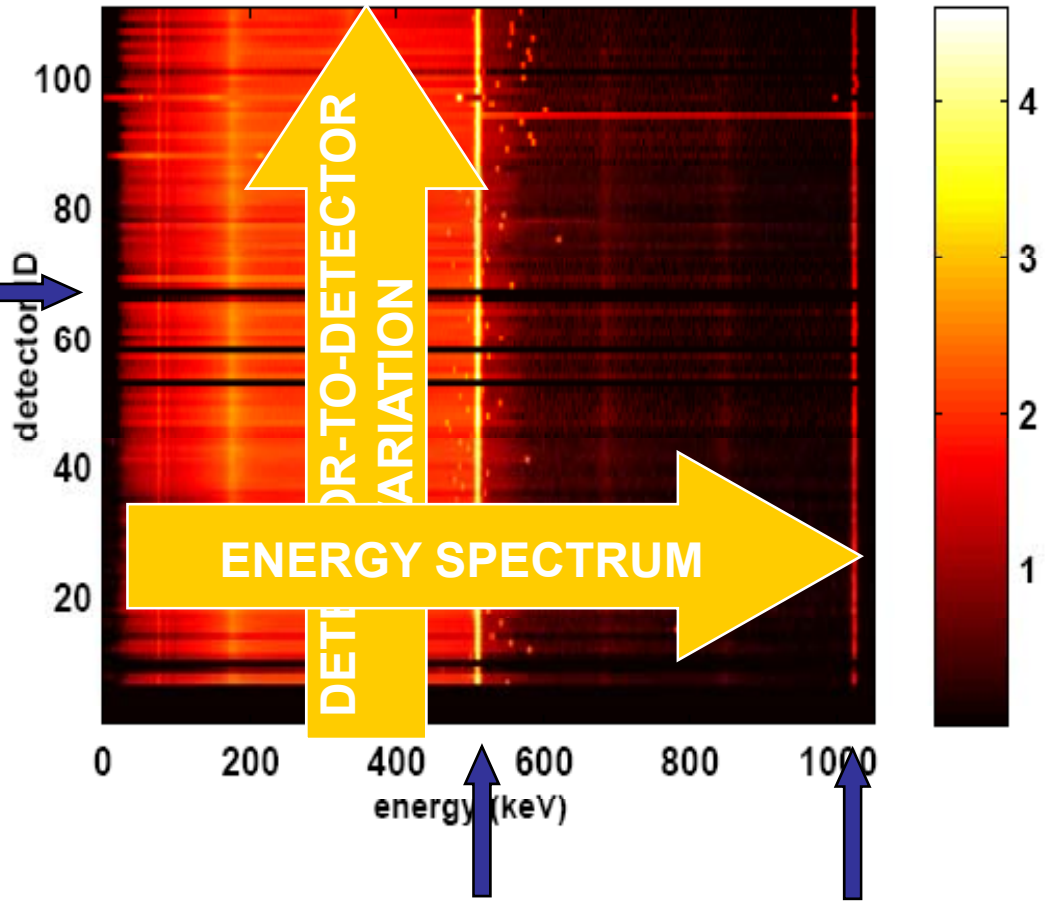


Fig. 3. The energy spectra reported by 110 individual detectors. The colourscale at each pixel denotes $\log_{10} N_{i,\epsilon}$, where $N_{i,\epsilon}$ is the number of hits in energy bin ϵ recorded by the ith detector. A horizontal line profile drawn across the map would be the energy spectrum for the specific detector. A vertical profile across the map would be the detector-to-detector variation for the specific energy bin. Only time-gated clean hits are counted. The summed peak at 1022 keV is three orders of magnitude lower than the 511 keV peak.

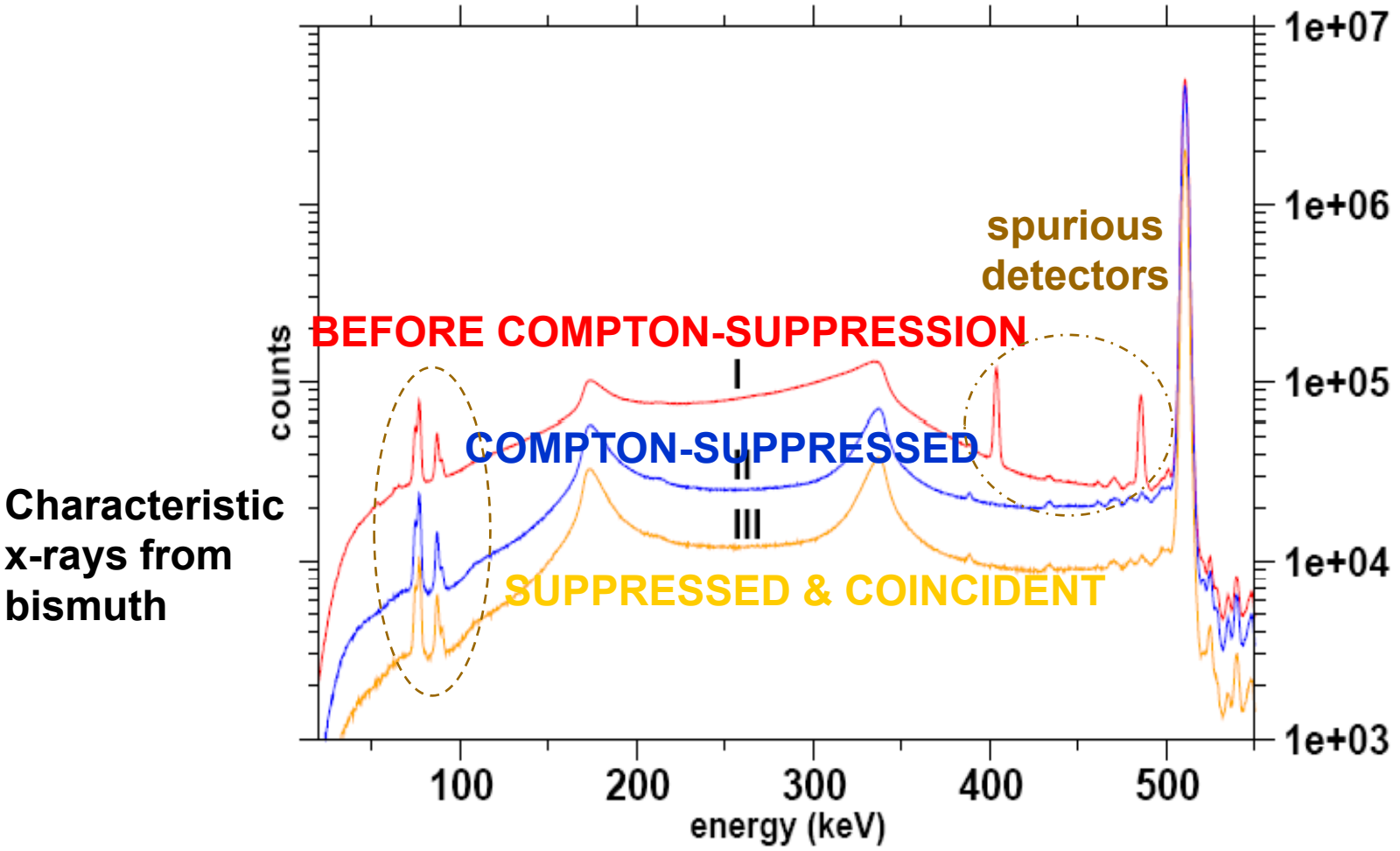
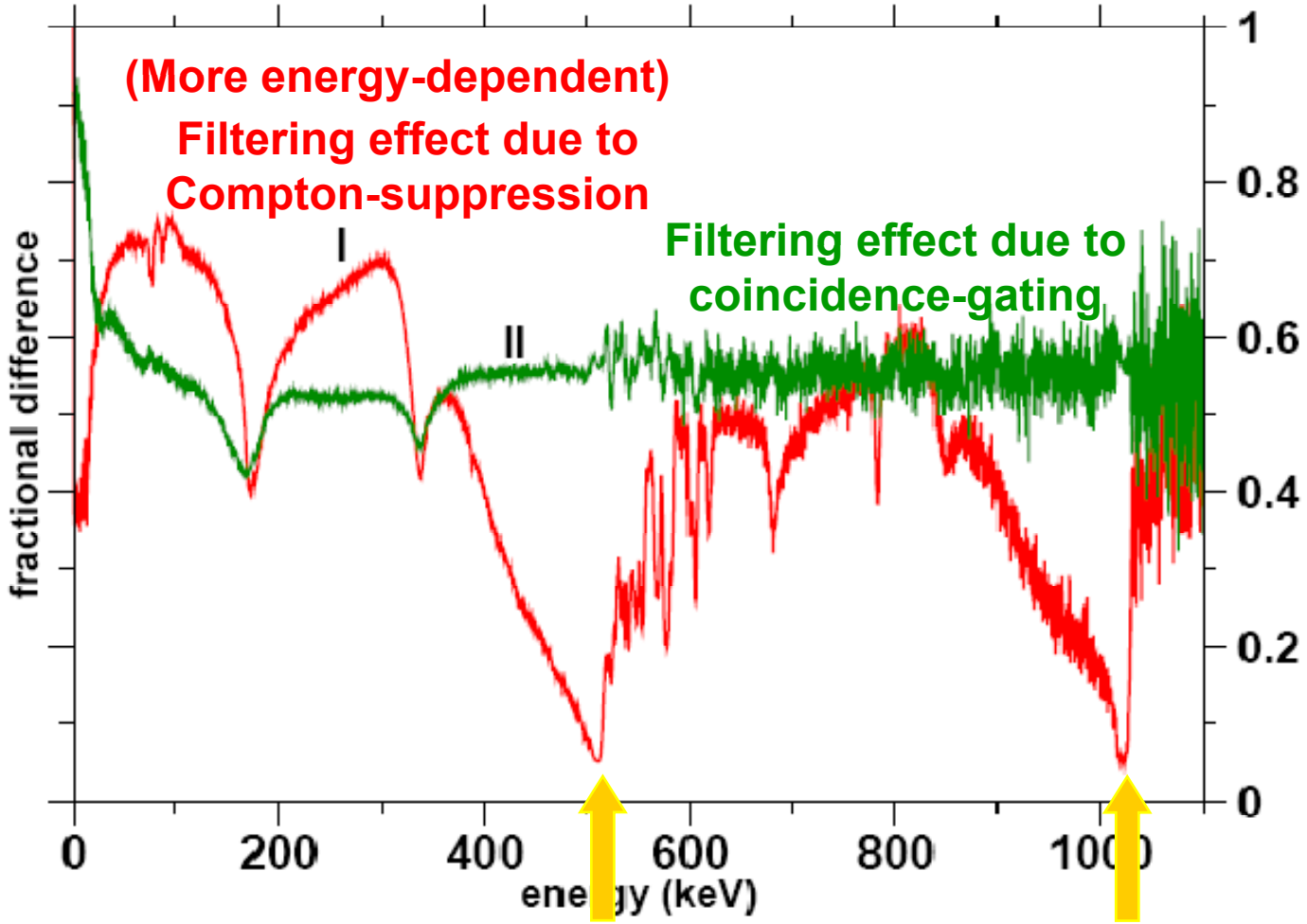


Fig. 1. Gamma spectra from the FDG source with the reference sample in place: (I) all hits from all detectors; (II) clean hits from non-outlying detectors only; (III) time-gated clean hits from non-outlying detectors only. The energy axis has been truncated.



FILTERED THE LEAST: FULL-ENERGY PHOTO-PEAK & SUMMED PEAK

Fig. 2. Variation in filtering effects with energy: fractional difference in counts per energy bin (I) with and without Compton-suppression; (II) before and after time-gating.

OURS versus OTHERS' 3γ WORK

^{18}F-FDG

CLINICAL SOURCE

MORE CHALLENGING

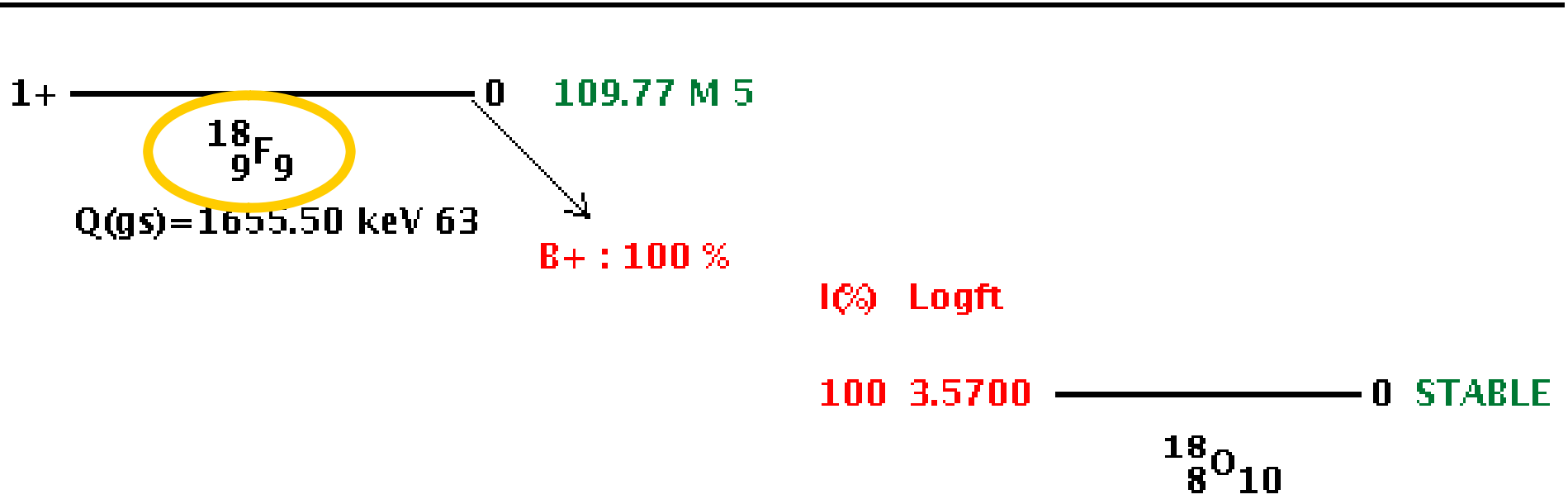
WE USED THIS

---

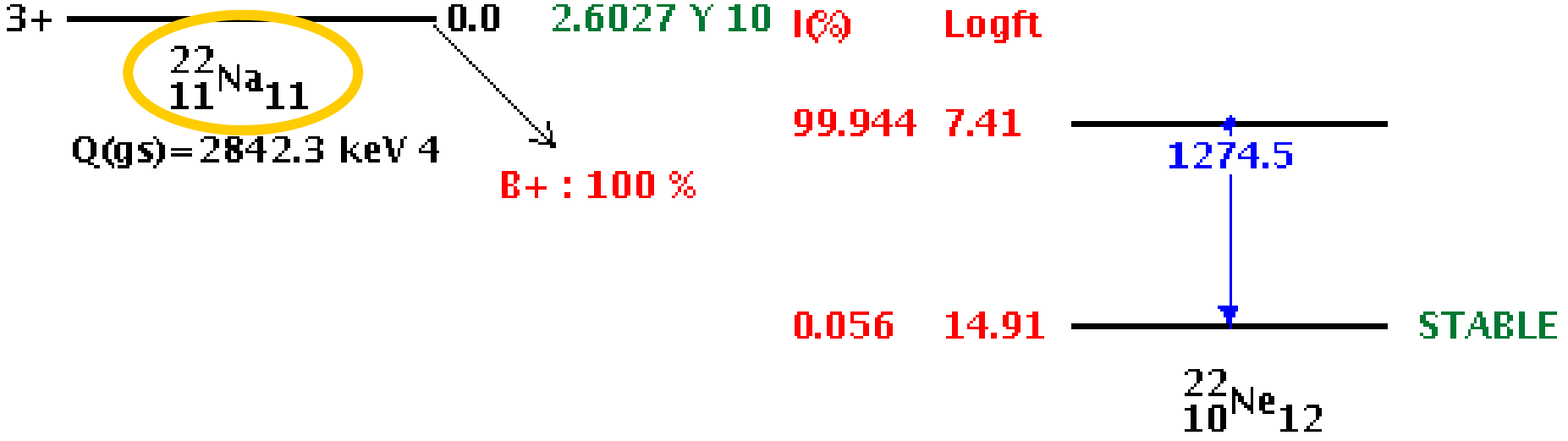
^{22}Na

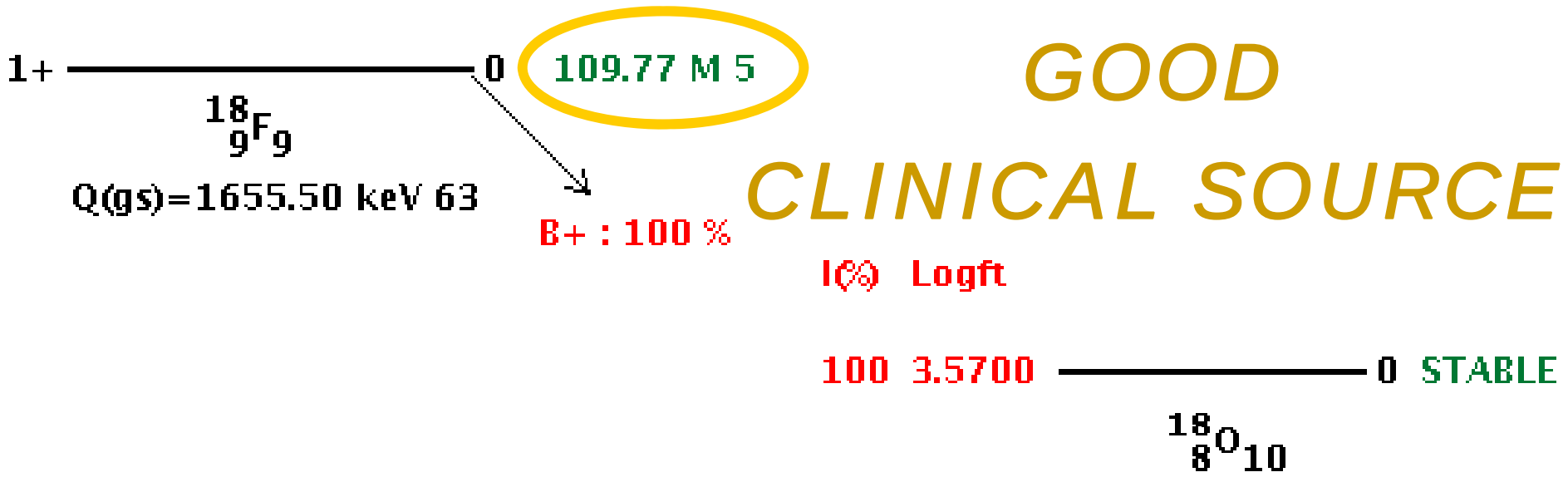
LABORATORY SOURCE

MORE CONVENIENT


1+
0
109.77 M 5
$^{18}_{9}F_{9}$
Q(gs)=1655.50 keV 63
B+ : 100 %
I(%) Logft
100 3.5700
0 STABLE
$^{18}_{8}O_{10}$

VERSUS


3+
0.0
2.6027 Y 10
$^{22}_{11}Na_{11}$
Q(gs)=2842.3 keV 4
B+ : 100 %
I(%) Logft
99.944 7.41
1274.5
0.056 14.91
STABLE
$^{22}_{10}Ne_{12}$



GOOD

CLINICAL SOURCE

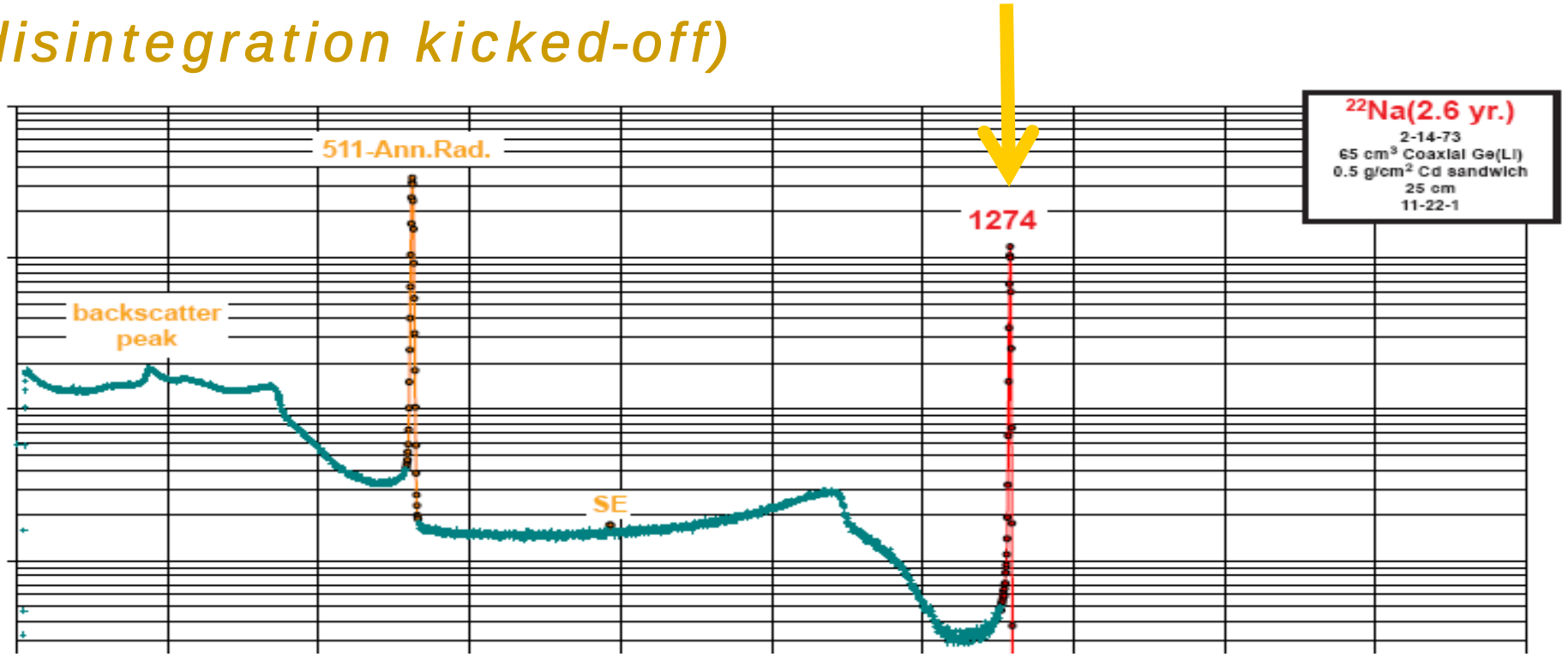
GOOD

LABORATORY SOURCE

THIS EXTRA PEAK (not found in ^{18}F)

- ALLOWS NORMALISATION BETWEEN 2 DATA ACQUISITIONS (we know how many disintegrations took place)

- PROVIDES REFERENCE TIME TRIGGER FOR LIFETIME MEASUREMENTS (we know when the disintegration kicked-off)

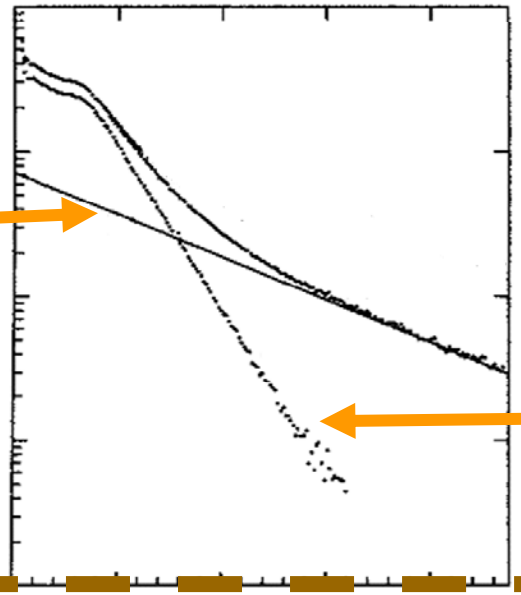


DETECTION OF 3γ/2γ YIELDS

SLOW COMPONENT

ORTHO-POSITRONIUMS

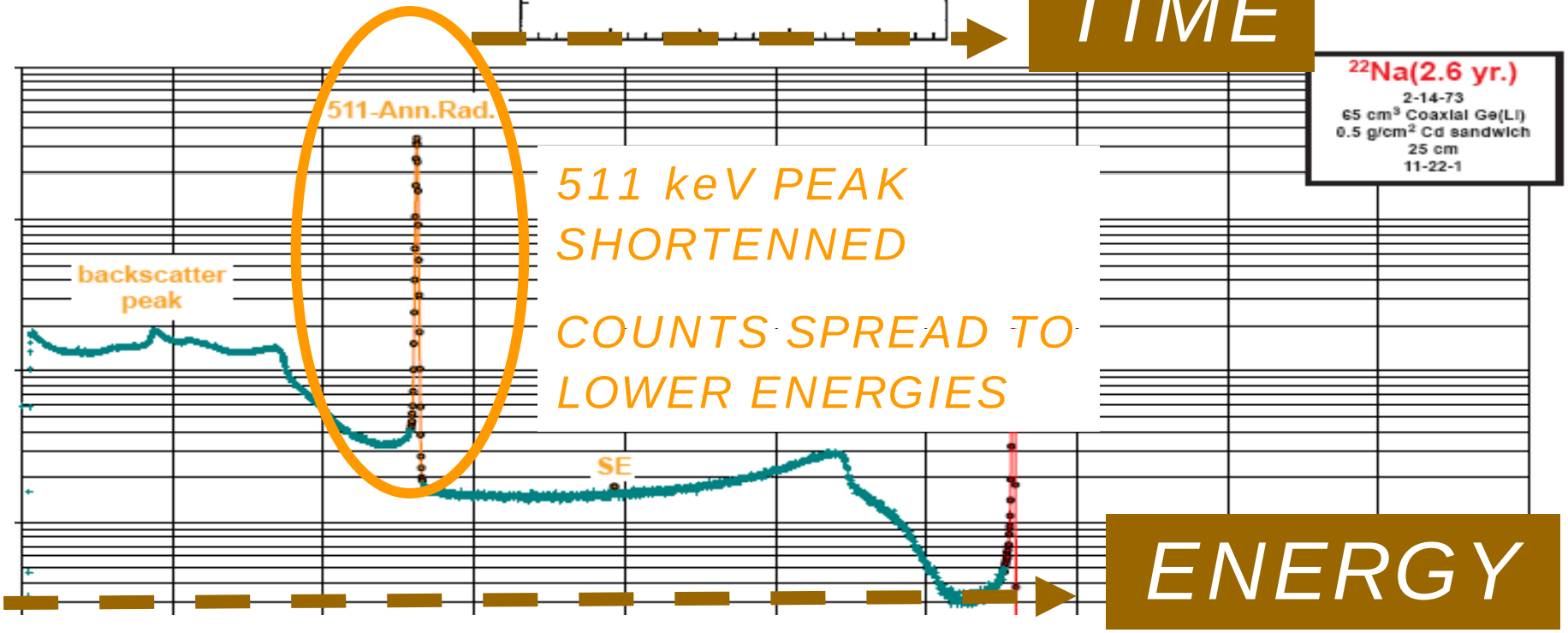
(3γ)



FAST COMPONENT

FREE POSITRONS

TIME



511 keV PEAK SHORTENNED

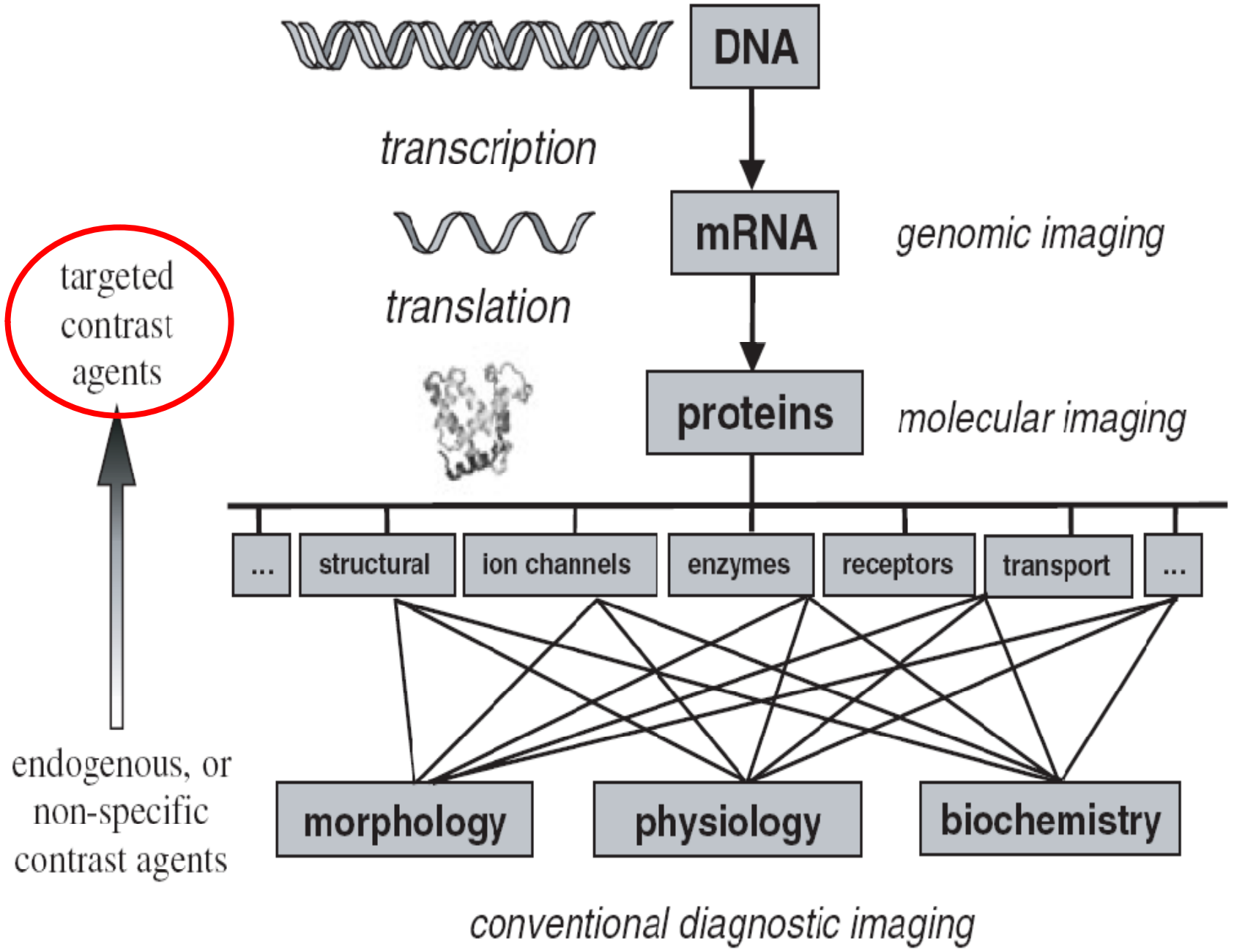
COUNTS SPREAD TO LOWER ENERGIES

ENERGY

TABLE I.—*Main non-invasive* in vivo *imaging modalities used in molecular and cellular imaging studies.*

Imaging modality	Form of energy used and variable assessed	Main imaging agent/contrast	Primary use	Type of information
Positron emission tomography (PET)	Annihilation photons Radioactivity distribution	^{18}F, ^{11}C, ^{15}O, ^{64}Cu, ^{124}I	Whole-body clinical and research applications	Physiologic cellular molecular
Single photon emission computed tomography (SPECT)	γ photons Radioactivity distribution	^{99m}Tc, ^{111}In, ^{123}I, ^{125}I, ^{201}Tl	Whole-body clinical and research applications	Physiologic cellular molecular
Bio-luminescence imaging (BLI)	Visible to infrared photons Luminescence	Firefly and Renilla luciferase	Reporter gene expression, cell tracking	Cellular molecular
Fluorescence imaging (FLI)	Visible to infrared photons Fluorescence	GFP, RFP, NIR fluorochromes. Quantum dots	Reporter gene expression, cell tracking,	Cellular molecular
Magnetic resonance imaging/spectroscopy (MRI/MRS)	Radiofrequency waves Tissue molecular composition	Chelated gadolinium, SPIO, Nanoparticles	Whole-body high contrast clinical general imaging and spectroscopy	Morphologic physiologic cellular
Computer tomography (CT)	X-rays Tissue density	Iodinated, blood pool contrast agent	Whole-body general imaging. Small animal phenotyping	Morphologic

REPRODUCED FROM LECCHI M et al Q J NUC MED MOL IMAGING 2007;51:111-26



REPRODUCED FROM CHERRY SR PHYS. MED. BIOL. 2004;49:R13-48

CONCLUSION

3γ/2γ *YIELDS ARE ABLE TO DIFFERENTIATE BIOLOGICAL SAMPLES*

THE METHOD IS SENSITIVE TO CHEMICAL SPECIES IN THE SAMPLES

3γ/2γ *YIELD DOES NOT DEPEND ON* O_2 *ALONE*

PROSPECTS NOT JUST FOR HYPOXIA-IMAGING ALONE BUT MOLECULAR IMAGING ON A WIDER SCALE

FURTHER WORK

TO INVESTIGATE THE DIFFERENT CONFOUNDING FACTORS PERTURBING $3\gamma/2\gamma$ *YIELDS*

DEAD TIME ISSUES

GAMMA-TRACKING INSTEAD OF COMPTON-SUPPRESSION

ACKNOWLEDGEMENTS

Dr K Kacperski carried out the experiments while he was employed as a post-doc by the University of Surrey

This work was supported in part by the US Department of Energy, Office of Nuclear Physics, under contract No. DE-AC02-06CH11357

	Total plasma N	Urea N	NPN	Amino N	Sugar	Inorganic phosphorus	Hemo-globin	Cell
	mg. %	*mg. %*	*mg. %*	*mg. %*	*mg. %*	*mg. %*	*gm. %*	*vol. %*
Cattle	1177.6 (2)	12.2 (2)	30.0 (27)	7.19 (36)	53.0 (39)	5.7 (2)	10.90 (52)	34.3 (36)
Horse	1296.0 (23)	18.7 (21)	25.8 (31)		109.0 (31)			33.0 (51)
Sheep	1054.4 (22)	13.0 (26)	28.5 (33)	4.76 (37)	63.90 (40)	7.1 (44)		
Dog	1131.2 (22)	11.7 (28)	30.8 (28)	6.70 (28)	82.00 (28)	3.5 (45)	14.11 (47)	47.7 (47)
Rabbit	1072.0 (23)	13.0 (26)	31.0 (32)		124.0 (43)	4.5 (46)		
Swine	1216.0 (22)	17.3 (29)	31.4 (34)		128.0 (34)		11.95 (48)	47.8 (48)
Rat	1040 (23)	15.6 (29)	42.0 (35)		122 (42)			48.0 (40)
Hen		4.53 (25)	38.5 (25)		212 (25)	3.96 (2)		
Cat	1347.2 (22)	30.3 (26)	52.6 (32)					
Man	1120 (24)	17.1 (30)	35.6 (30)	6.40 (38)	112.0 (30)			45.6 (50)
Goat*	1128	22.31	48.52	9.60	59.1	7.70	9.26	28.8

REPRODUCED FROM HOUCHIN OB et al J. DAIRY SCI. 1939;22:241-50

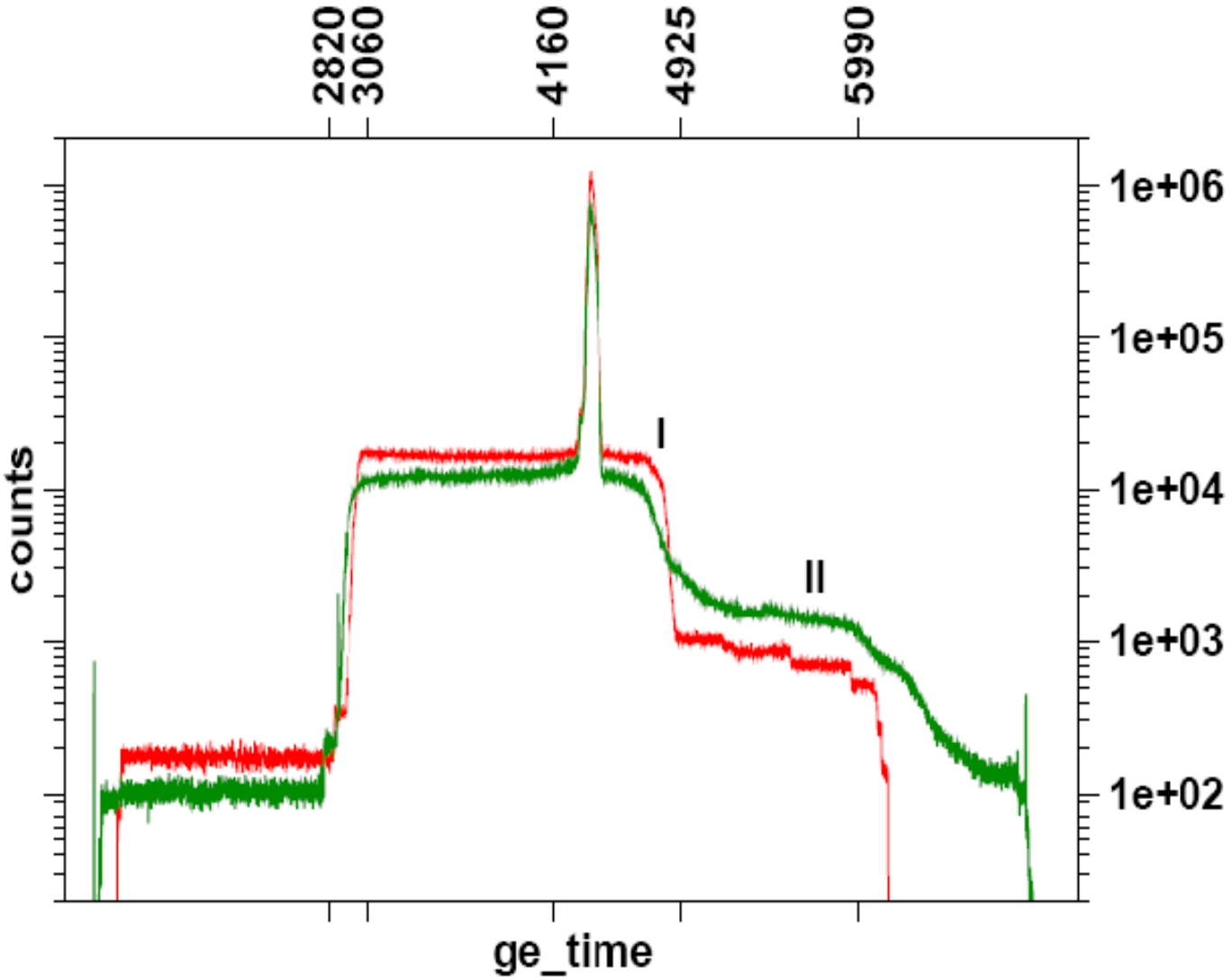


Fig. 4. Time spectra of (I) clean hits and (II) dirty hits. The FWHM of the peak is equivalent to $\sim$5 ns. Hits from outlying detectors were not counted.