PET Quantification

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Positron Emission Tomography: Principles and Instrumentation

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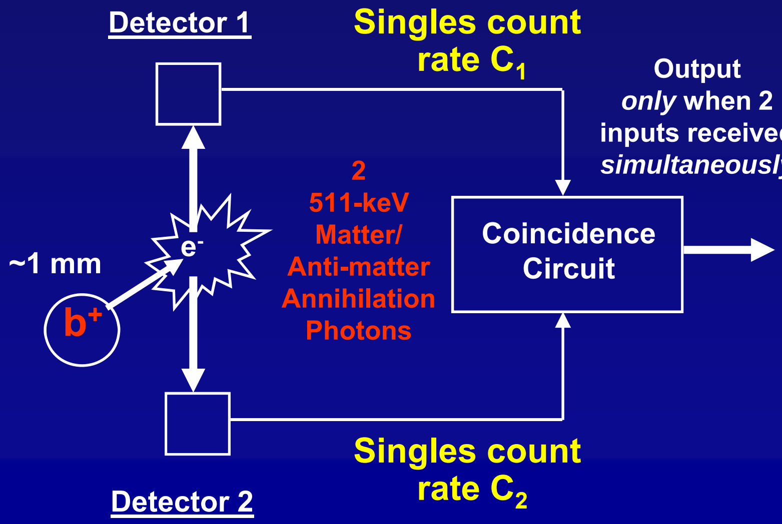
References: Zanzonico P. Sem Nucl Med 34: 87-111, 2004
Zanzonico P. Crit Rev Eukaryot Gene Expr 16: 61-101, 2006

Positron Emission Tomography (PET)

"Tomogram" = "picture of slice"

β+
(511 keV γ-rays)
emitters
eg F18

Coincidence Detection



Detector 1

Singles count rate C_1

Output *only* when 2 inputs received *simultaneously*

~1 mm

b^+

e^-

2 511-keV Matter/ Anti-matter Annihilation Photons

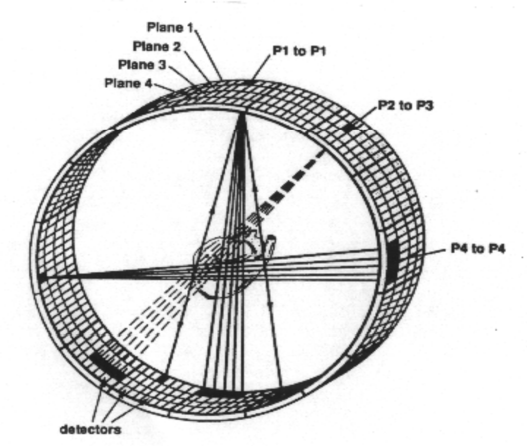
Coincidence Circuit

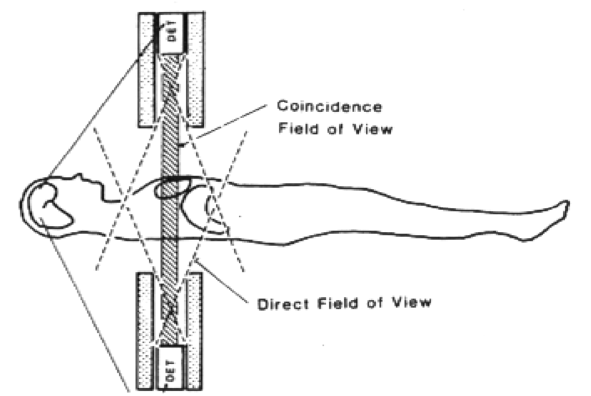
Singles count rate C_2

Detector 2

2 inputs received within same *coincidence timing window* τ
10 nsec = 1×10^{-8} sec

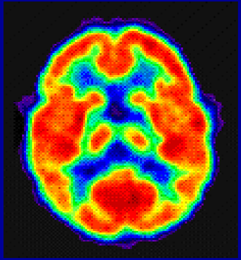
→ "Trues" Count Rate $= C_1 C_2 \tau$



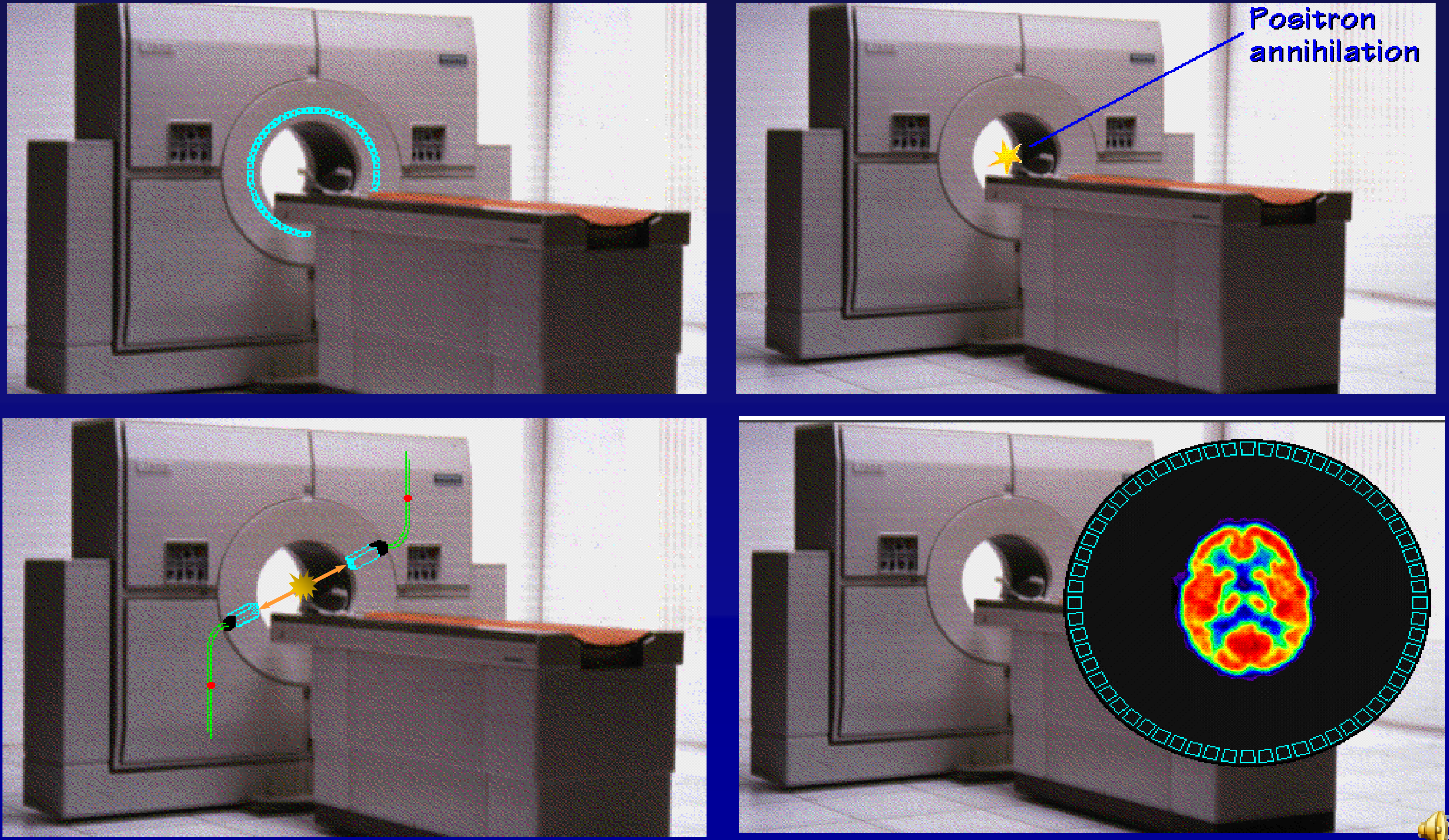


Acquire data spanning 15-25 cm of the body at each of 6-8 bed positions for ~6 min each – emission data and transmission data for attenuation correction

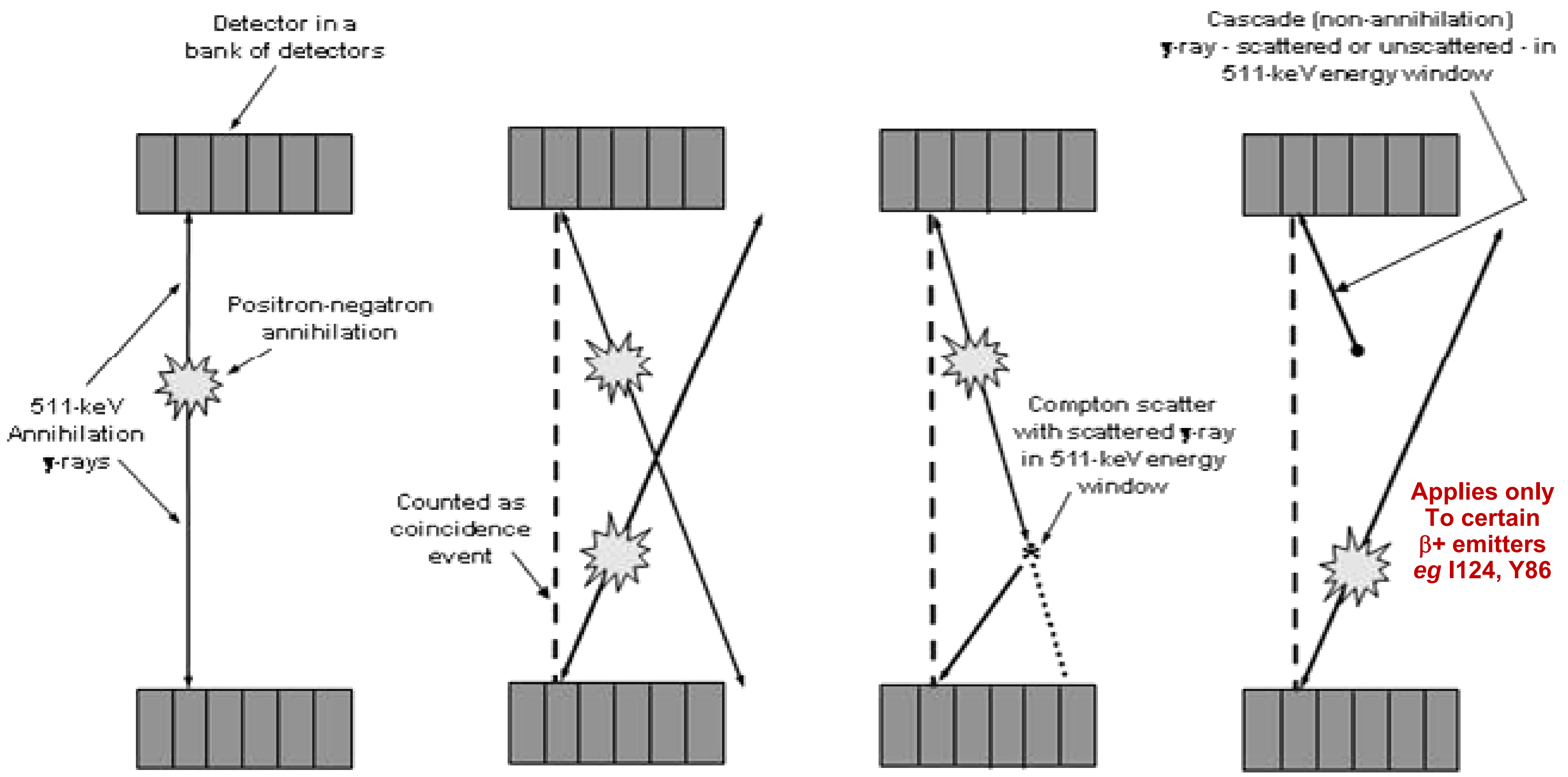
Images are quantitative (μCi/cc or SUV)



PET Scanners



“Events” in PET



Detector in a bank of detectors

Positron-negatron annihilation

511-keV Annihilation γ-rays

Counted as coincidence event

Compton scatter with scattered γ-ray in 511-keV energy window

Cascade (non-annihilation) γ-ray - scattered or unscattered - in 511-keV energy window

Applies only To certain β+ emitters *eg* I124, Y86

True Coincidence (“True”)

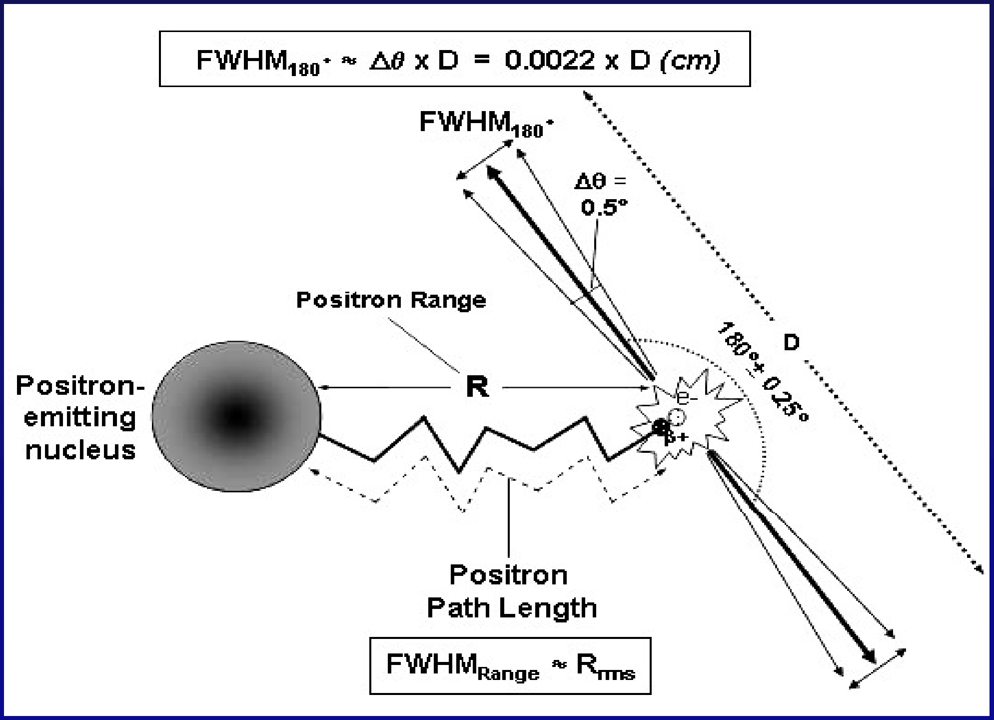
Random or Accidental Coincidence (“Random”)

Scattered Coincidence (“Scatter”)

Spurious Coincidence

Physical Limitations of PET

① **Energy-dependent positron R_{rms}:**
0.76 mm for F18 to 9.8 mm for Ga66
Lower limit of PET resolution?

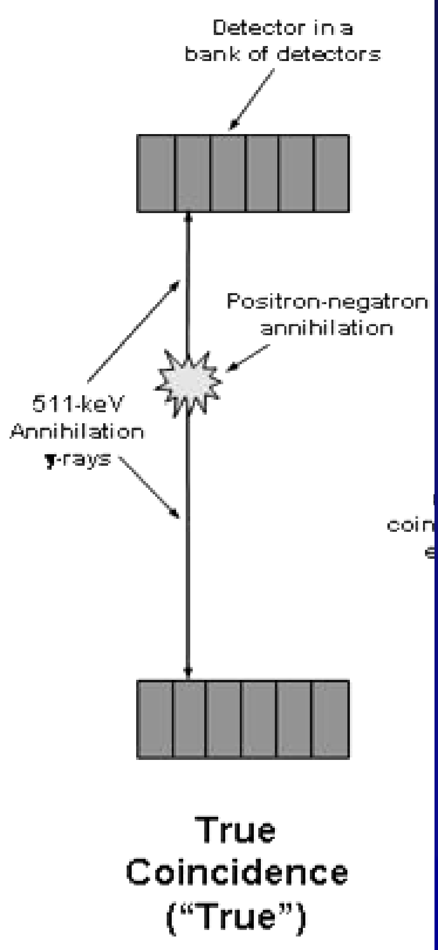


② $\vec{p}_{positron} + \vec{p}_{negatron} \neq 0 \Rightarrow$

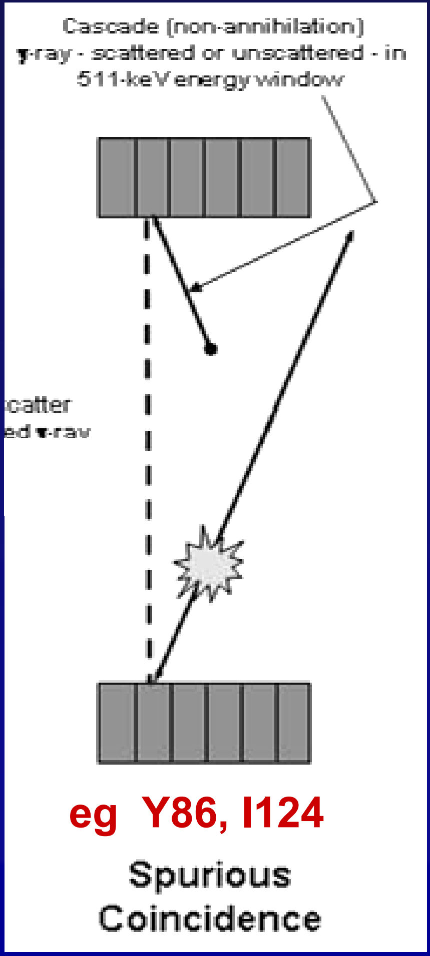
Annihilations γs: deviate from 180° by ± 0.25°

The larger the PET ring diameter, the worse the degradation of resolution
WB > Brain > Small animal

③ **Cascade γ-rays**



True Coincidence ("True")



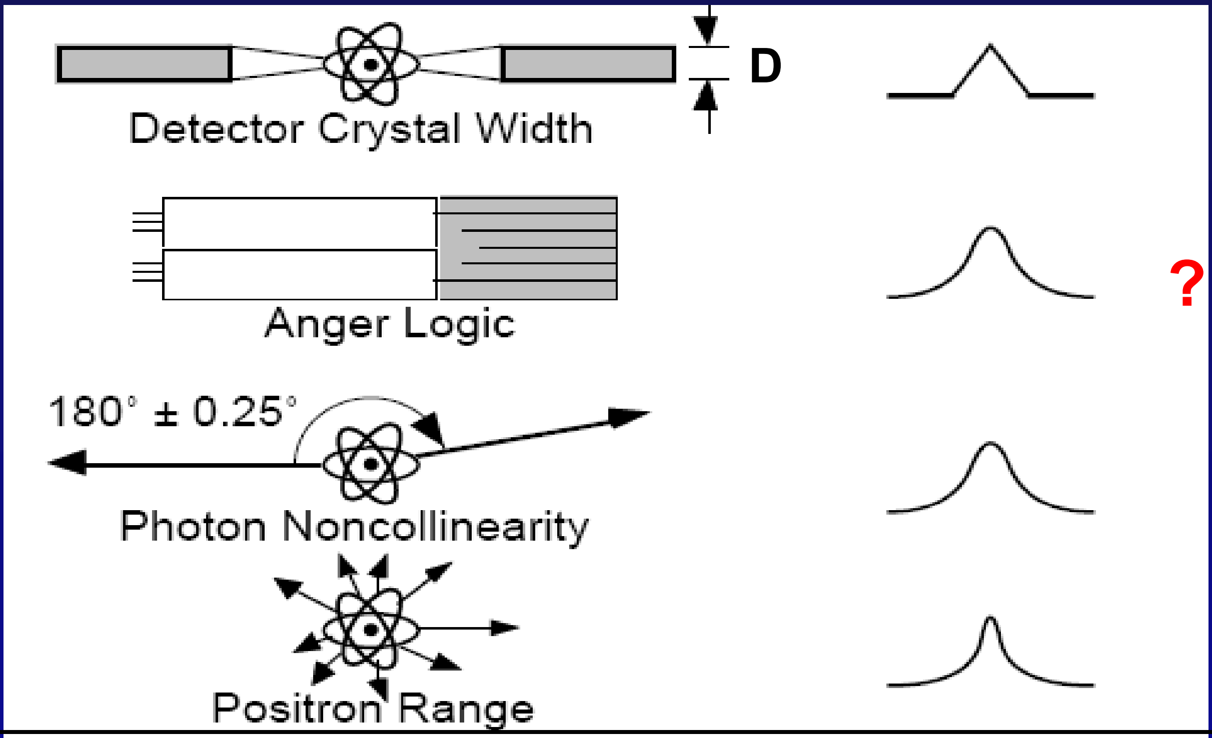
eg Y86, I124

Spurious Coincidence

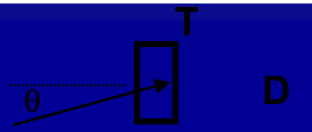
④ **Low β+ Branching Ratio**

Determinants of Spatial Resolution

~4 mm FWHM for F18



Factor	*Shape*	*FWHM Contribution*
Detector Crystal Width		d/2 - 1.5 mm
Anger Logic	?	0 - 1 PMT/detector 2.2 mm - 4 PMTs/detector (Anger logic)
Photon Noncollinearity		1.3 mm - Head 2.2 mm - Body
Positron Range		0.2 mm - F18 3.3 mm - Ga66



DOI

multiplicative factor

~2

$\cos\theta + (D/T)\sin\theta \approx$

X1.3 for $\theta = 10°$

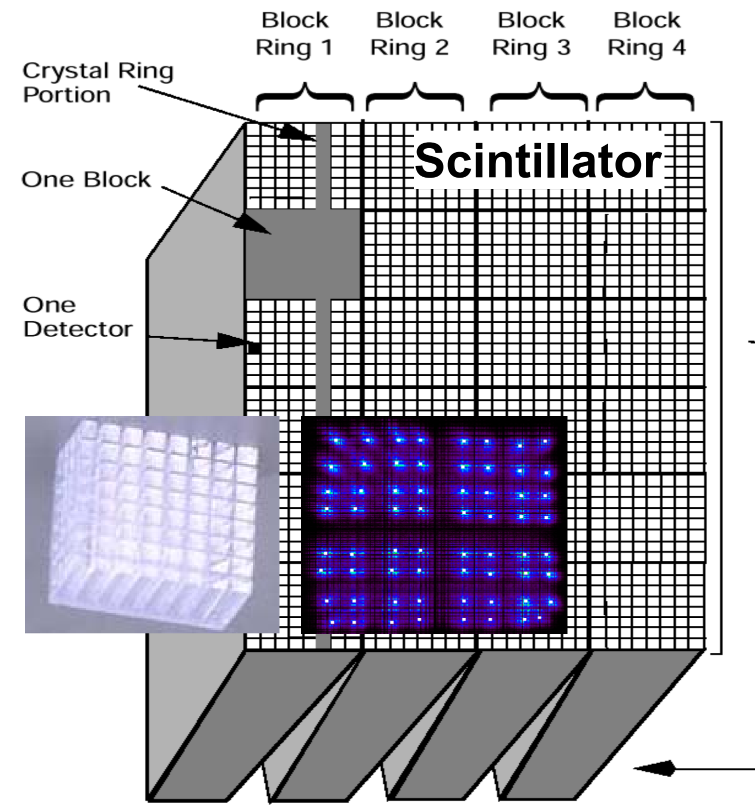
reso by

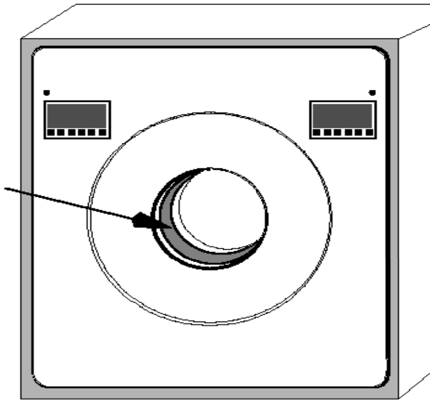
Reconstruction Algorithm	multiplicative factor	X1.2

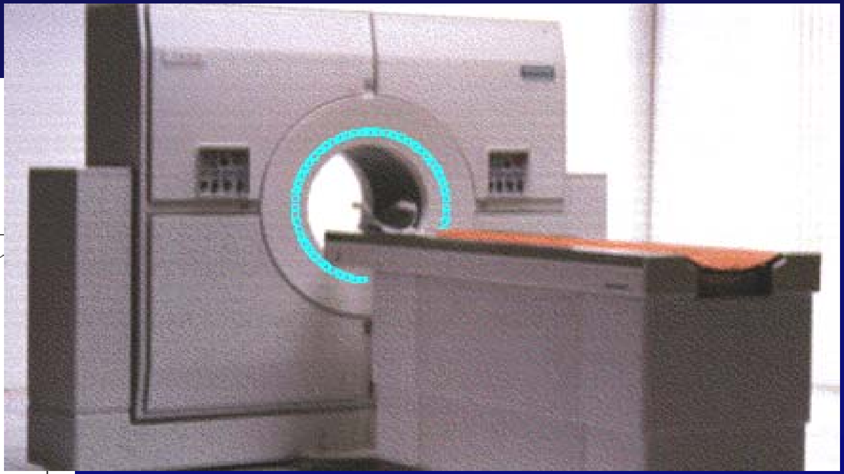
~6 mm FWHM for F18

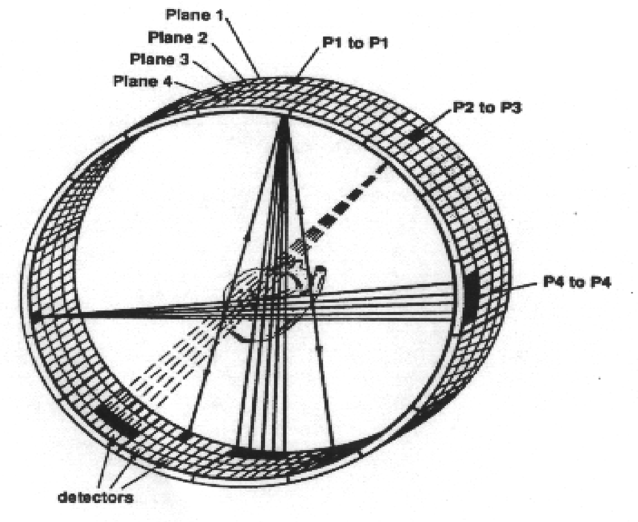
PET Detector Configuration

Cylindrical Multi-ring Block Detector *







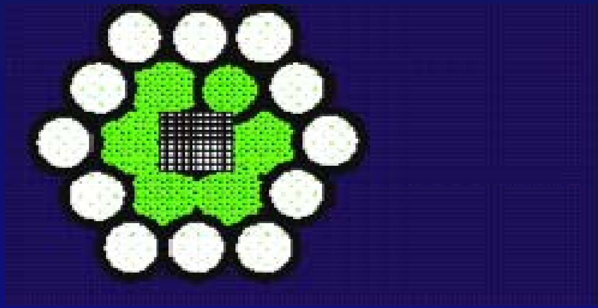


* Most common dedicated PET scanner design

Newer Design in PET Systems

The Pixelated "Continuous"-Detector Scanner

Pixelated Detector

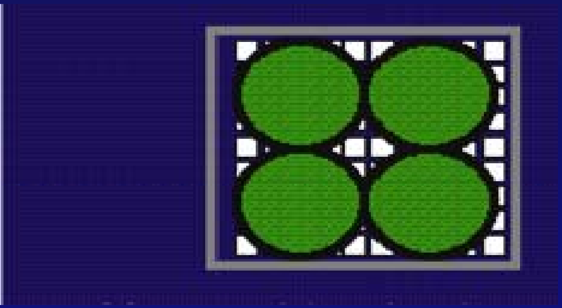


"Designed for 3D PET"

<20% variation in light collection

Phillips
Allegro PET,
Gemini PET-CT

Block Detector



"Designed for 2D PET"

>100% variation in light collection

Siemens/CT
HR+, Accel, PET
Biograph PET-CT
GE
Advance PET,
Discovery LS/ST

Modern Block-Detector PET Scanners

Detector rings: ~4

Blocks per ring: 100 *to* 200

Scintillator thickness, T: ~1 cm

Cuts per scintillator: 6-8

Detector elements per scintillator: 6 x 6 = 36 *to* 8 x 8 = 64

Detector element size, D: 3 x 3 *to* 6 x 6 mm

Detector ring (bore) diameter: 80 *to* 90 cm

Transaxial field of view (FOV): 50 *to* 70 cm

Axial (longitudinal) field of view (FOV): 20 *to* 30 cm

Transaxial sections: ~50

Transaxial section thickness: 2 *to* 4 mm

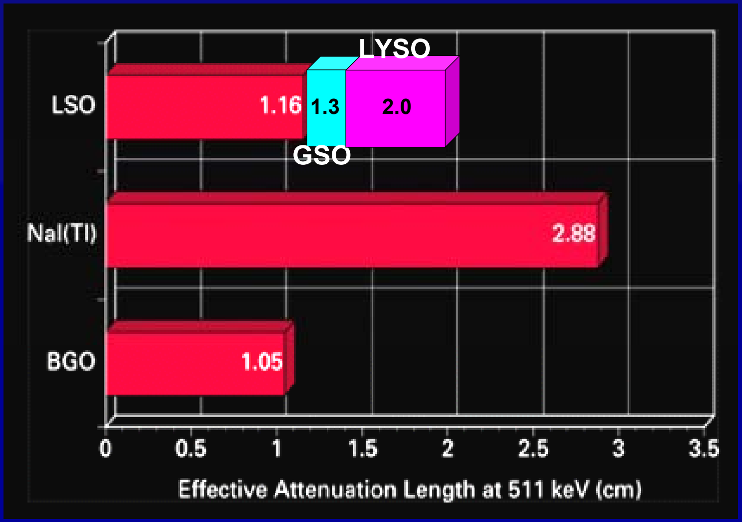
Near limit of affordable current technology

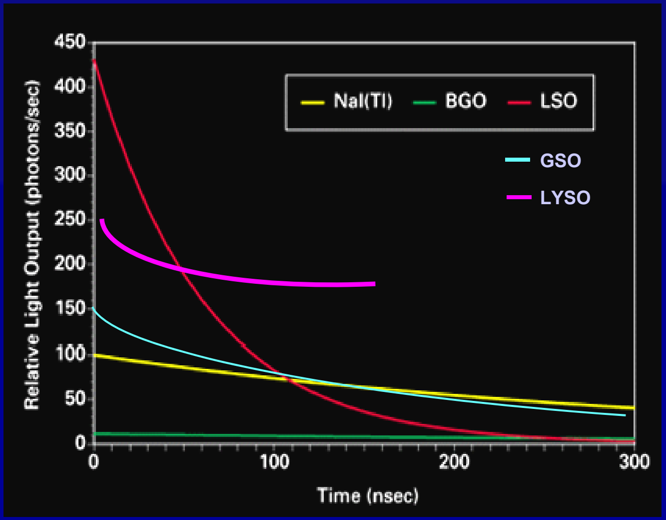
Current-Generation PET Scanners

• *Spatial Resolution*	4-6 mm FWHM
• *Sensitivity*	2D - <100 cps/μCi 3D - ~500 cps/μCi
• *Energy resolution*	20 - 40%
• *Axial field of view*	25 cm
• *Transaxial field of view*	60 cm
• *Attenuation Correction*	PET-CT
• *Scatter Correction*	2D √ 3D ?
• *Reconstruction*	OSEM RAMLA
• *Absolute Quantitation*	√

Comparison of PET Detector (Crystal) Materials

	BGO Bismuth Germanate oxysilicate	LSO Lutecium Ortho-oxysilicate	GSO Germanium Ortho Ortho-	LYSO Lutecium-Yttrium oxysilicate
Mass density, ρ	7.1	7.4	6.7	5.4
Effective atomic number, Z_{eff}	74	66	59	54
Light decay time, τ	300 nsec	40 nsec	60 nsec	50 nec
Light output. η	4.8 /keV	30 /keV	6.4 /keV	30 /keV
E Resolution (FWHM)	~25%	~20%	~15%	~20%





PET: Breaking the 10-min Barrier?

~60 /day

~20 /day

~10 /day

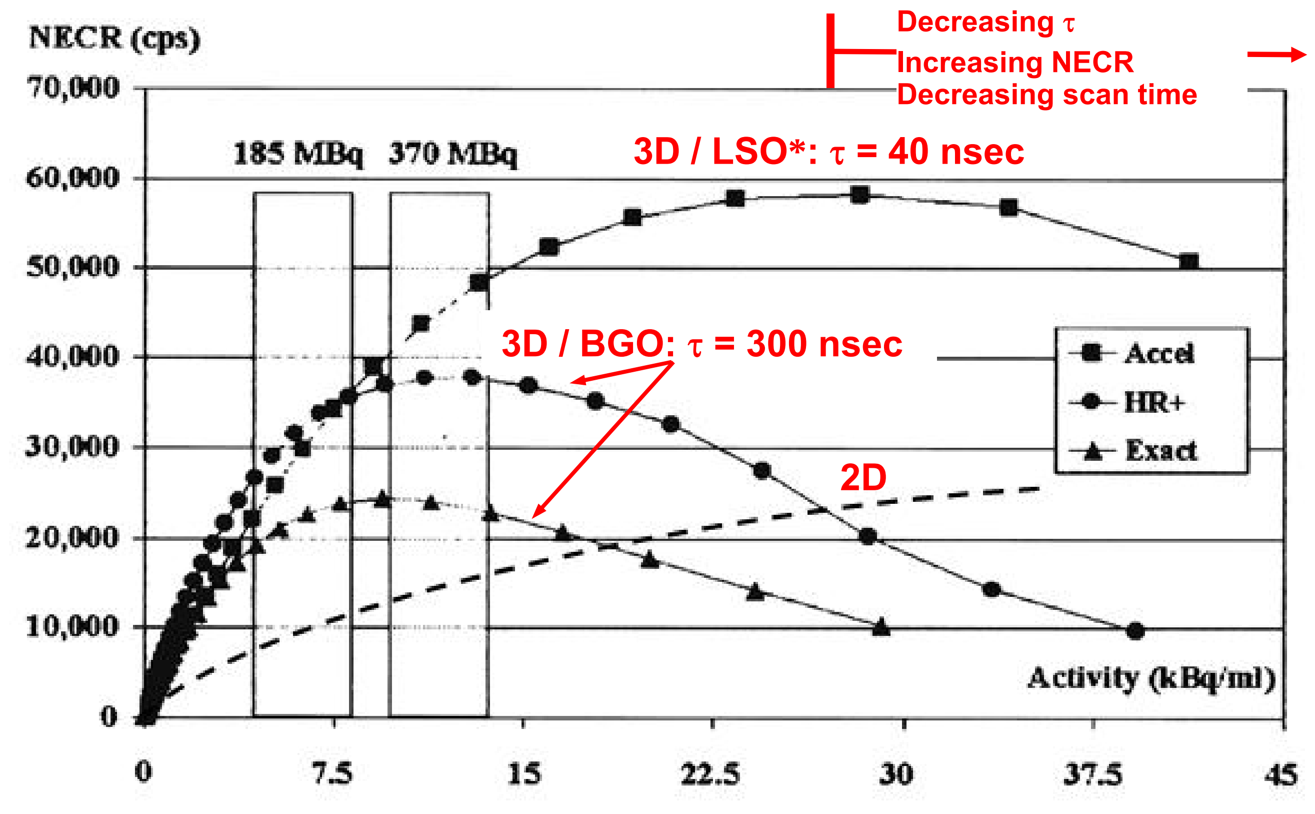
Patient Throughput

~10 min

~30 min

~60 min

WB Scans



Tarantola, Zito *et al*. J Nucl Med 44: 756, 2003.

- **New faster detectors?** **AA ≈ 40 mCi?**
- **Longer axial FOV?**

~10 cGy
max normal-tissue
absorbed dose

* GSO: τ = 60 nsec
LYSO: τ = 50 nsec

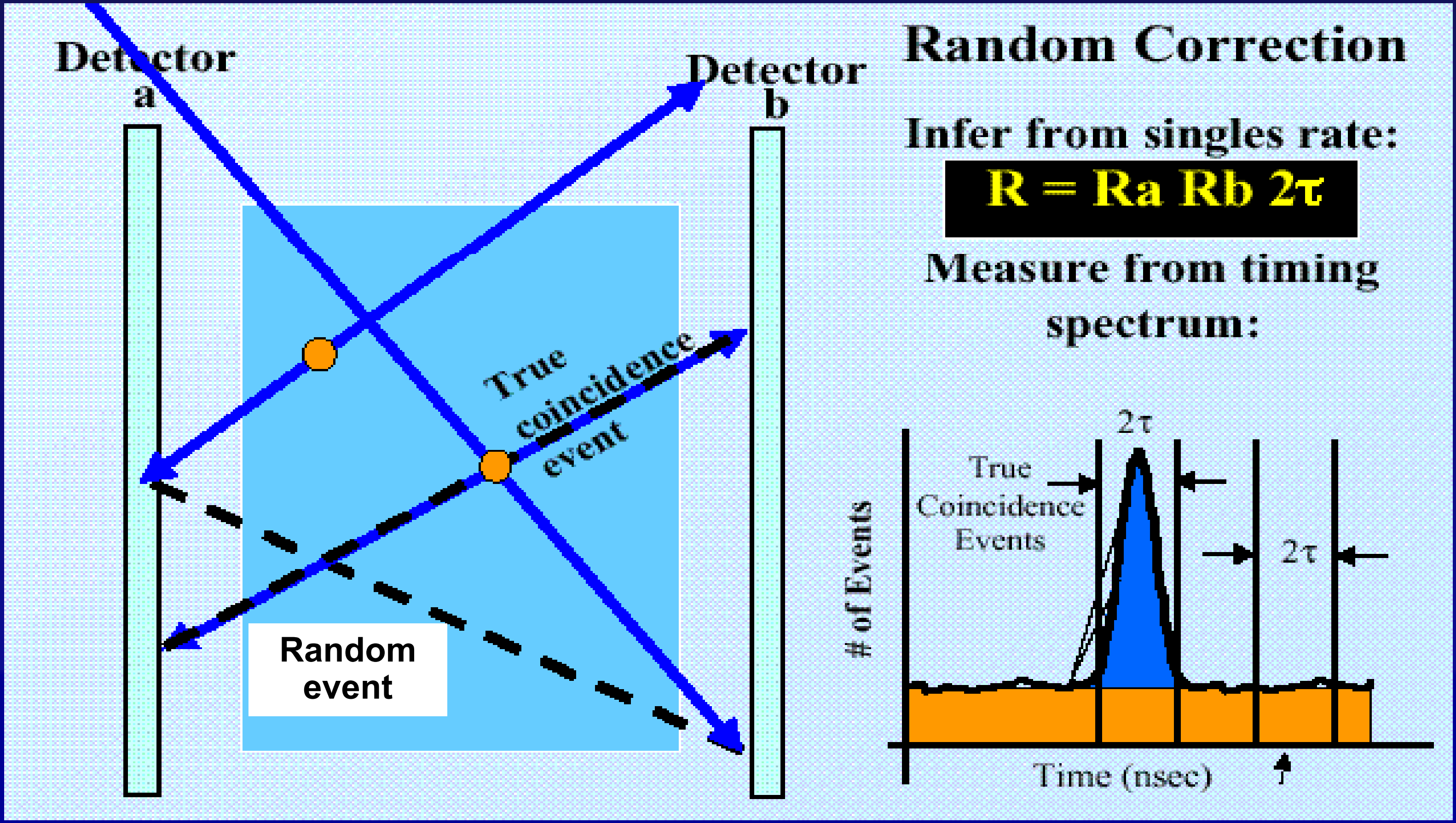
Corrections in PET *

- Randoms
- Attenuation
- Scatter

* Essential for activity quantitation
Generally applied to Sinogram data, *not* Reconstructed images
In contrast to SPECT, corrections are *independent* of depth (position)

Corrections in PET

Randoms Correction



Random Correction

Infer from singles rate:

$$R = R_a R_b 2\tau$$

Measure from timing spectrum:

Most events detected in PET are randoms

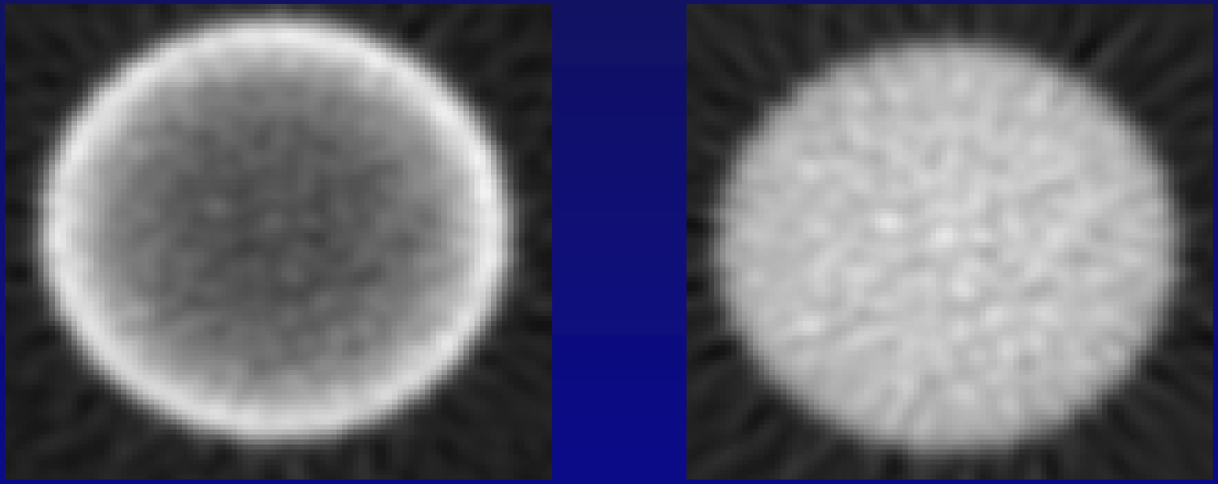
Corrections in PET

Attenuation

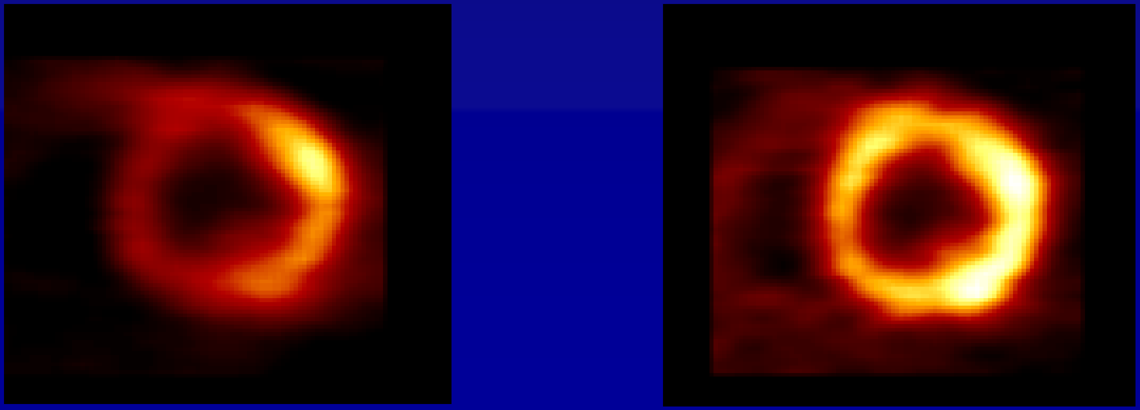
<u>*Uncorrected*</u>

<u>*Corrected*</u>

Cylinder uniformly filled with F18
Transverse image

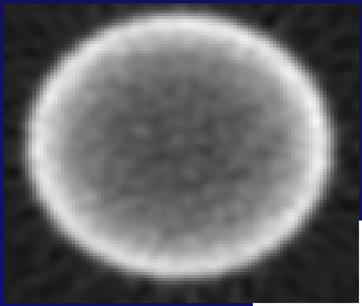


Rb82 Myocardial Perfusion Study
Short-axis image of left ventricle



Attenuation and Attenuation Correction

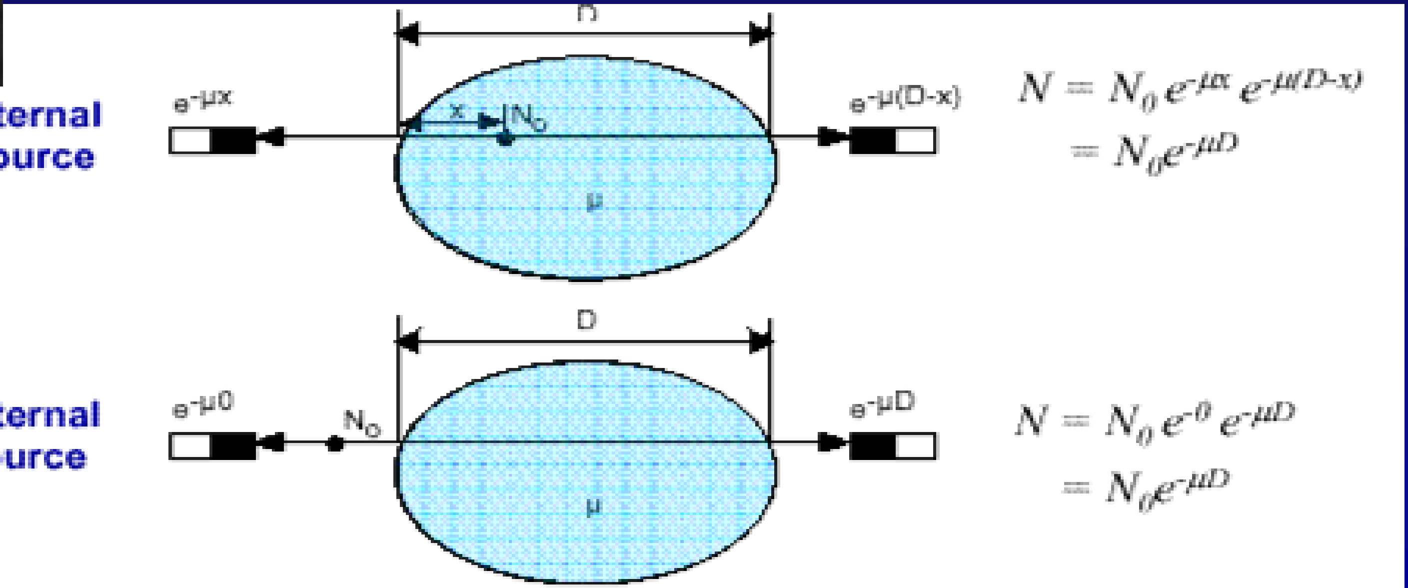
Attenuation is *independent* of position (depth) along the LOR



Uncorrected

Internal source

External source



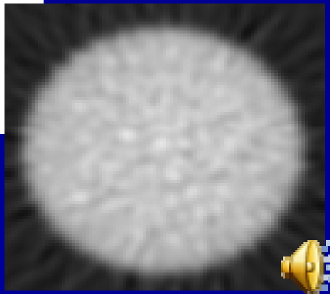
$$N = N_0 e^{-\mu x} e^{-\mu(D-x)} = N_0 e^{-\mu D}$$

$$N = N_0 e^{-0} e^{-\mu D} = N_0 e^{-\mu D}$$

Attenuation Correction Factor ACF = N_0/N

N_0 is unattenuated count, N is attenuated count of transmission source

Corrected



Attenuation Correction (AC) in PET

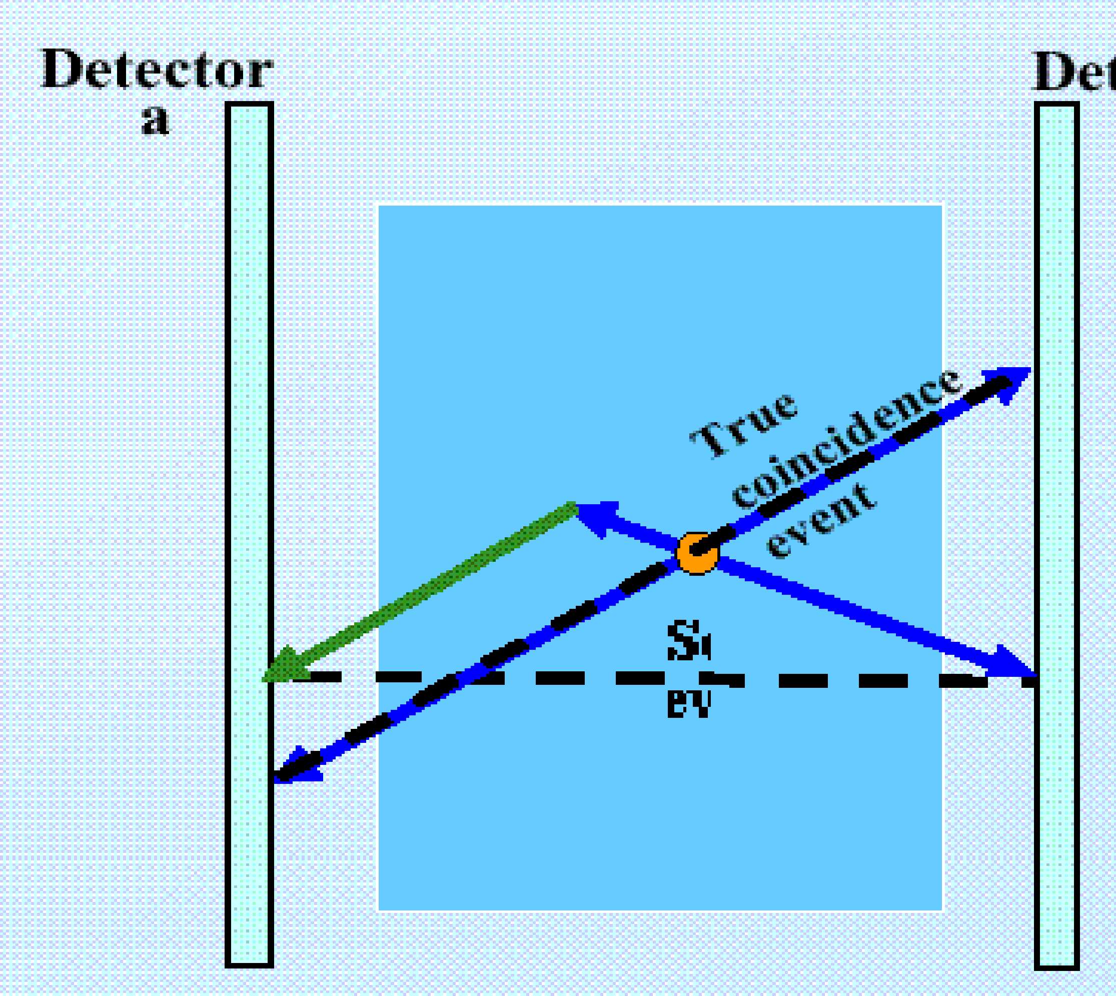
- **Transmission scan**
  - ~~β+-emitting Ge68/Ga68 sources - *$10K /yr to replace*~~
  - ~~Single-photon-emitting Cs137 sources - *No replacement*~~

    ~~Requires good E resolution to separate 667-keV Cs137~~
    ~~γ-rays from the 511-keV annihilation photons - GSO~~
  - CT (PET-CT)
    - Conversion of HUs - 140-kVp/~80 keV μ_s *to* 511-keV μ_s

      "Scaling factor" *different* for air (Lung), water
      Soft tissue), calcium (Bone), and barium (Contrast)
    - Contrast via enema yields artifactually high activities in bladder / intestinal lumen but *not* soft-tissue lesions
- **Segmentation**
  - ~~Use transmission scan to delineate Lungs (air) vs Bone vs Soft tissue and calculate AC based on tissue-specific μ~~

Corrections in PET

Scatter



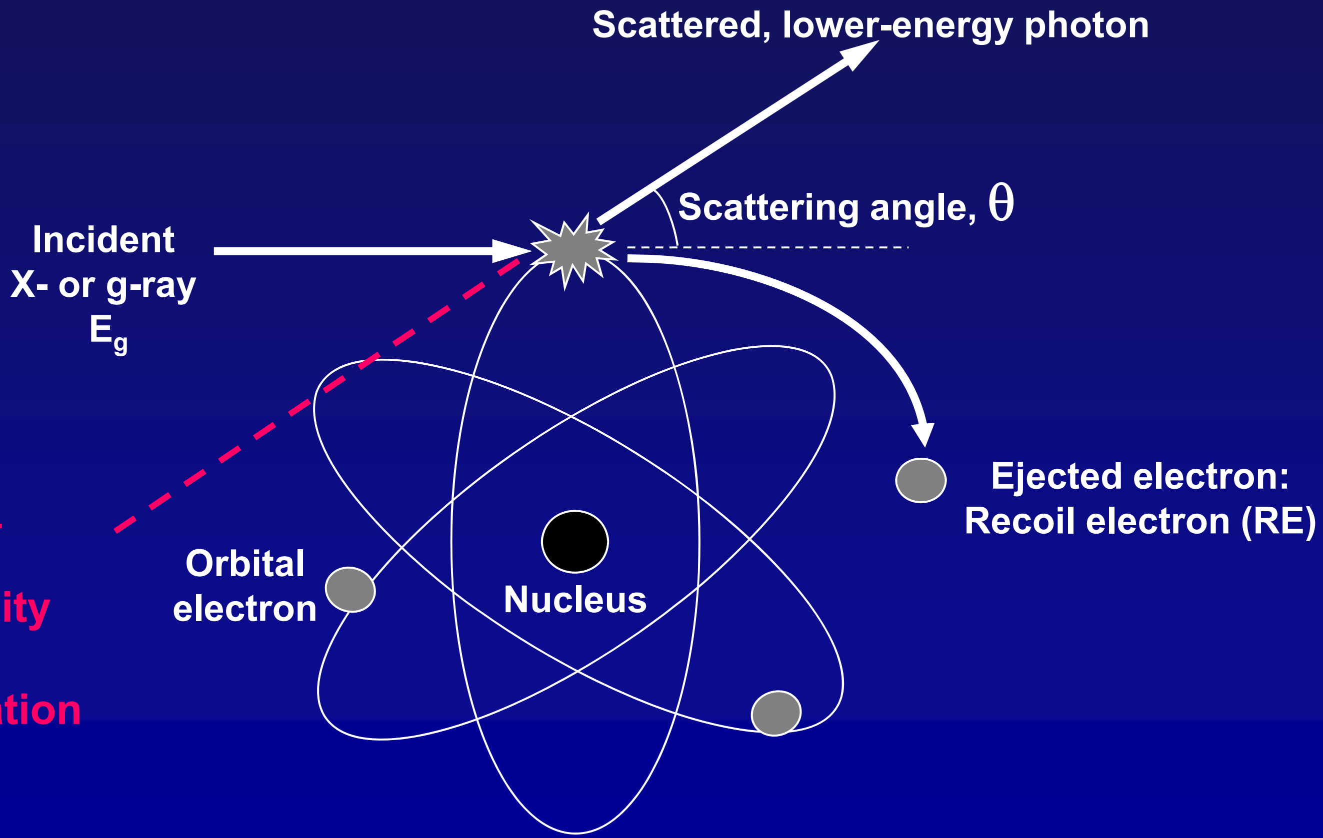
Scatter Correction

2D: Energy discrimination
Background subtraction

3D: More complicated

Compton Scatter

Incident photon does not disappear
but is scattered with a lower energy



Scattered, lower-energy photon

Scattering angle, θ

Incident
X- or g-ray
E_g

Ejected electron:
Recoil electron (RE)

Orbital
electron

Nucleus

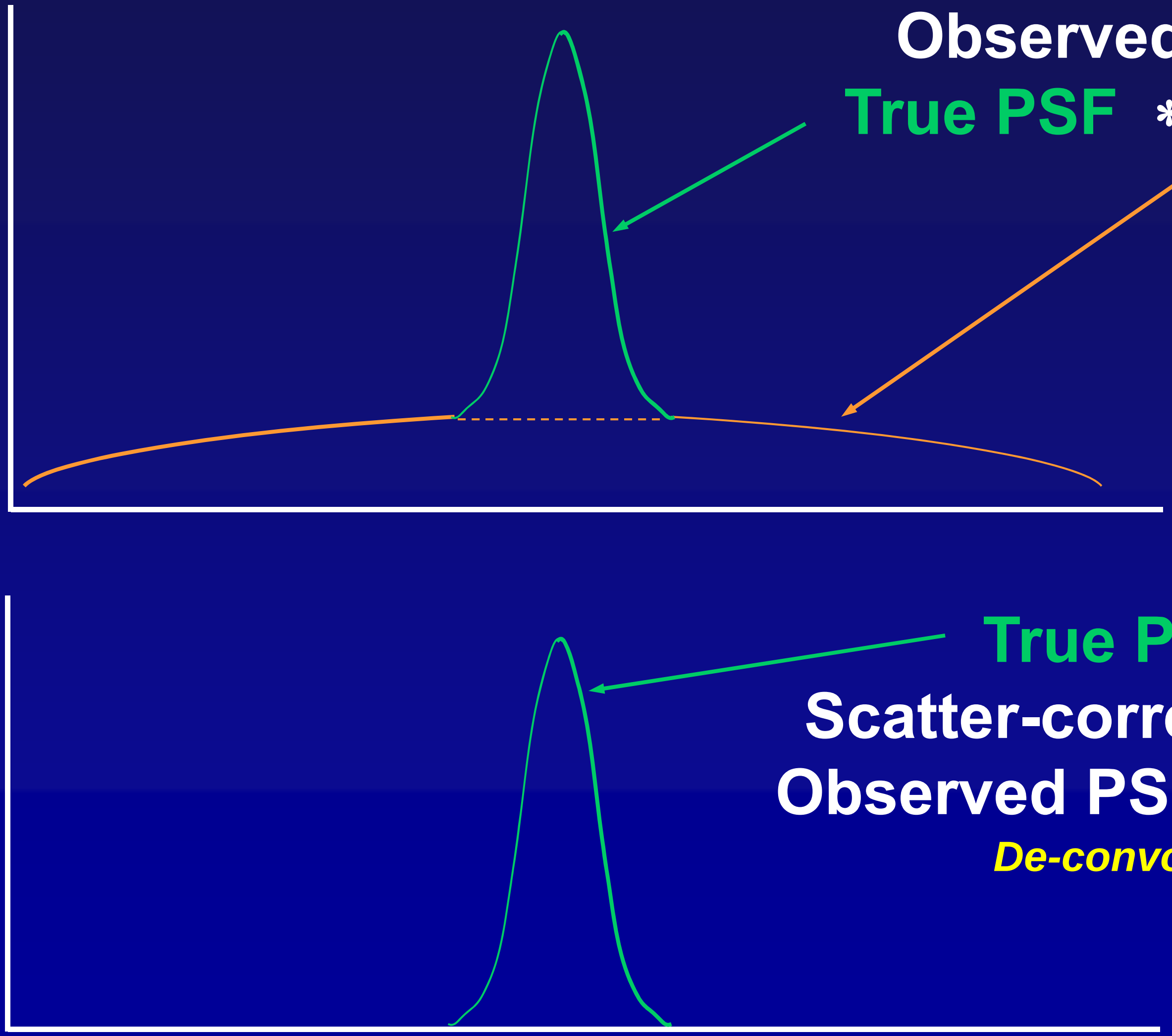
Major problem in
radionuclide imaging

- *Mispositioned Counts*
  Degrade image quality
- *"Extra" Counts*
  Complicate quantitation

PET detector materials such as BGO and LSO have poor energy resolution - up to 50% - compared to only 10% for NaI(Tl) used in gamma cameras ⇒ Requires use of "wide" photopeak energy windows, 250-650 keV, in PET

Corrections in PET

Scatter Correction



Observed PSF =
True PSF ∗ Scatter

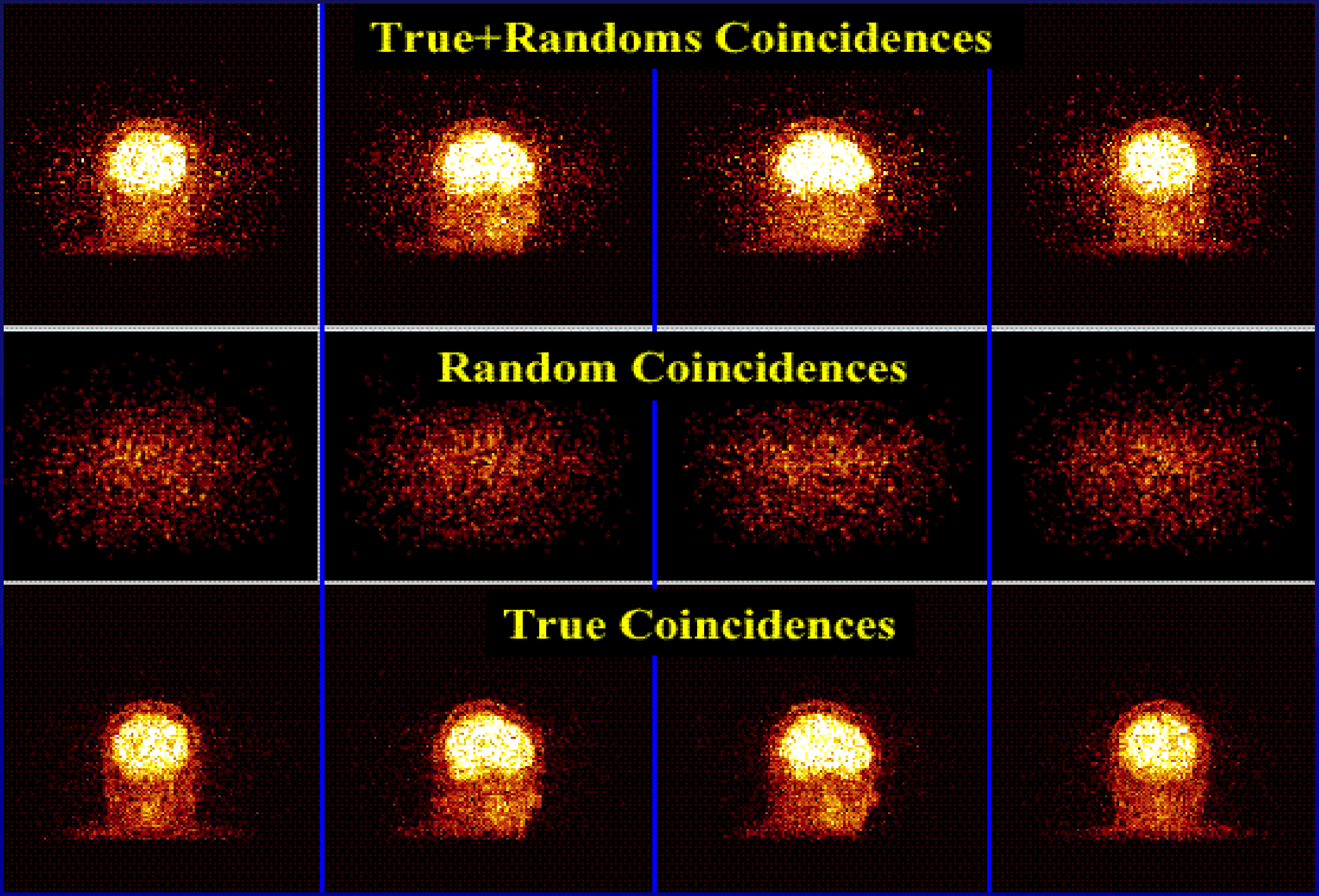
PSF:
Point-Spread
Function
(in 1 dimension)

True PSF =
Scatter-corrected PSF =
Observed PSF ∗ Scatter^{-1}

De-convolution

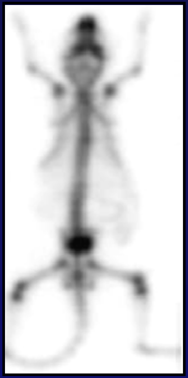
Corrections in PET

Randoms / Scatter Corrections



Reconstruction Algorithms in PET

- **2D Algorithms** - **Current** (GE, Siemens/CTI)
  - Filtered back-projection, Iterative (OSEM)
  - Requires 2 resolution-degrading steps
    1) 3D re-binning
    2) 2D re-binning



- **3D Algorithms** - **Current** (Philips)
  - Row-action maximization-likelihood algorithm (RAMLA)
  - Eliminates resolution degradation associated with re-binning 3D data into 2D projects

- **Modeling (including statistics) algorithms** - **Developmental**
  - *Maximum a posteriori* (MAP)
- **List-mode algorithms** - **Developmental**
  - Eliminates resolution degradation associated with re-binning list-mode data into 3D data *and* 3D data into 2D projections

Image Reconstruction Algorithms in PET

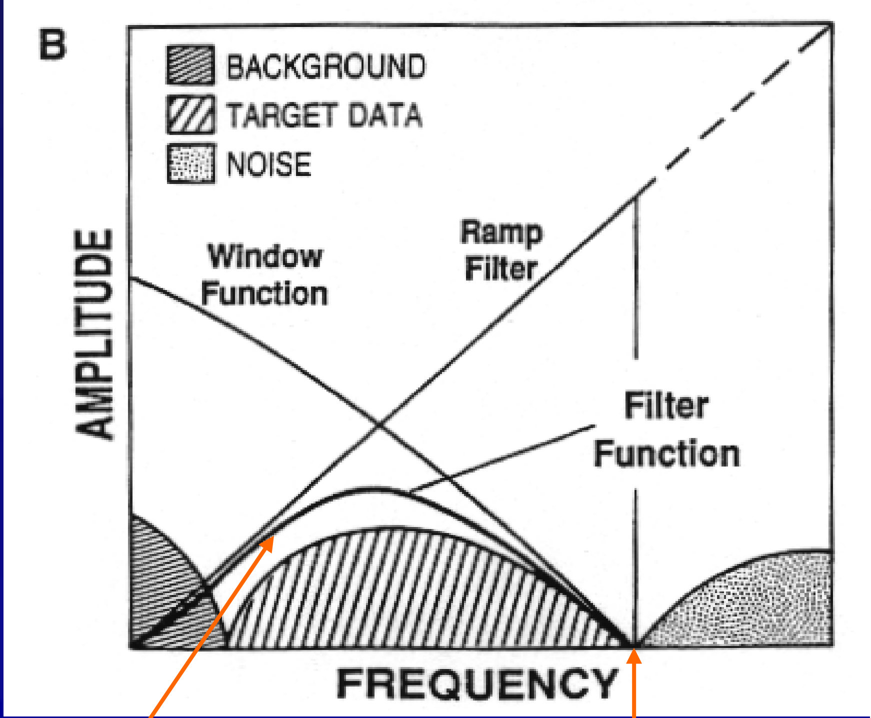
Filtered Back-Projection

- Widely used
- Fast
- Prone to “starburst” artifacts around“hot spots” (*eg* bladder)

Iterative Reconstruction

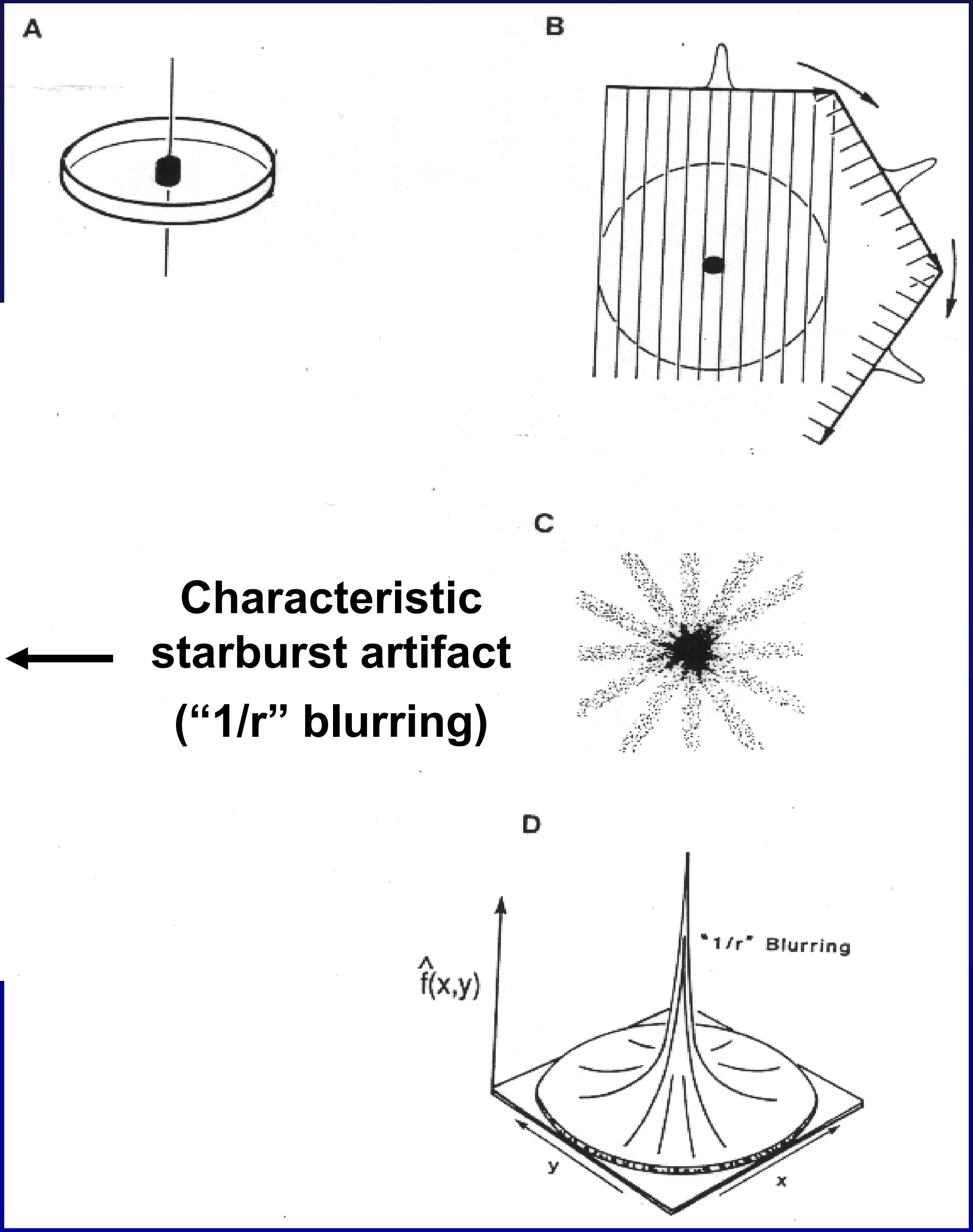
- Serial “guesses” (iterations) at correct solution
- Slow - Feasible clinically only with latest “fast” computers
- “Better” image quality / No “starburst” artifacts
- More accurate corrections for attenuation, scatter, detector response *etc*

Filtered Back-Projection (FBP)



Shape
(Hanning, Hamming,
Butterworth, Parzen *etc*)

Cut-off Frequency, ν_c
The lower the ν_c, the less noisy but the coarser resolution are the images



Characteristic starburst artifact (“1/r” blurring)

Iterative Reconstruction

- Iteration 1 = Uniform activity (or count) image <u>or</u>
  Filtered back-projection image *(Preferred)*

- Iteration n image = Iteration (n-1) image + *Back-Projection* [Projection data - Iteration (n-1) image projection]

- "Convergence" (reconstruction complete):
  [Projection data - Iteration n image projection]
  is <u>not</u> significantly less than
  [Projection data - Iteration (n-1) image projection]

- Typically converges in 4 iterations - Further iterations will make reconstructed images "noisier"

Iterative Reconstruction Algorithms

- Expectation Maximization (EM)

  At each iteration, maximize the logarithm of the probability that the image reconstructed at that iteration is the "correct" image.

- Maximum likelihood Expectation Maximization - MLEM
  - ♦ Apply all raw data (projection images) simultaneously to expectation maximization
  - ♦ Converges slowly

- Ordered Subset Expectation Maximization - OSEM
  - ♦ Apply only a part (sub-set) at a time of projection data (projection images over a specified angular interval) to expectation maximization)
    - "Level" = # of sub-sets
  - ♦ Converges 10X faster than MLEM

Absolute Quantitation with PET

$$\frac{\overset{\textit{Corrected for Randoms, Attenuation, and Scatter}}{\text{Count Rate (cps) / Voxel in Reconstructed Images}} \bullet e^{\lambda(t_{image} - t_{inj})}}{\underset{\textit{Measured}}{\text{F18 Calibration Factor (cps/}\mu\text{Ci)}} \bullet \text{Branching Ratio} \bullet \Delta x\ \Delta y\ \Delta z\ \text{mm}^3\text{ / voxel}} = \mu\text{Ci / mm}^3$$

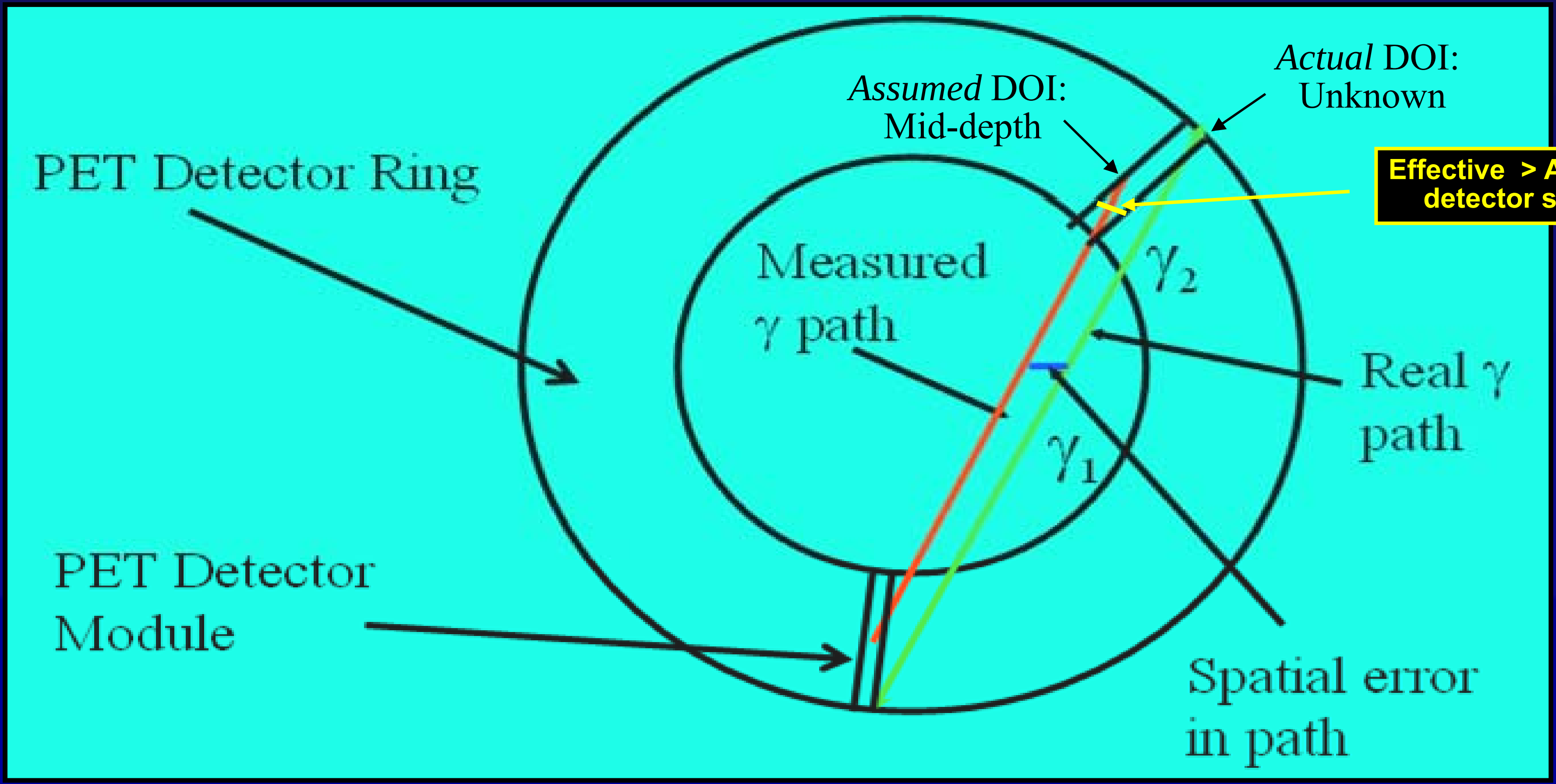
$$\frac{\mu\text{Ci / mm}^3 \bullet 100\%}{\text{Administered Activity (mCi)} \bullet 1{,}000\ \mu\text{Ci / mCi} \bullet 1\text{ gm / mm}^3} = \%\text{ ID / gm}$$

$$\frac{\mu\text{Ci / mm}^3}{\dfrac{\text{Administered Activity (mCi)}}{\text{Body Mass (kg)} \bullet 1{,}000\text{ gm / kg}} \bullet 1{,}000\ \mu\text{Ci / mCi} \bullet 1\text{ gm / mm}^3} = \text{Standard Uptake Value (SUV)}$$

Physical Limitations of PET *cont*

⑤ Depth-of-Interaction (DOI) Effect

*Degrades spatial resolution **



* Worsens towards periphery of FOV *and* for smaller-FOV tomographs

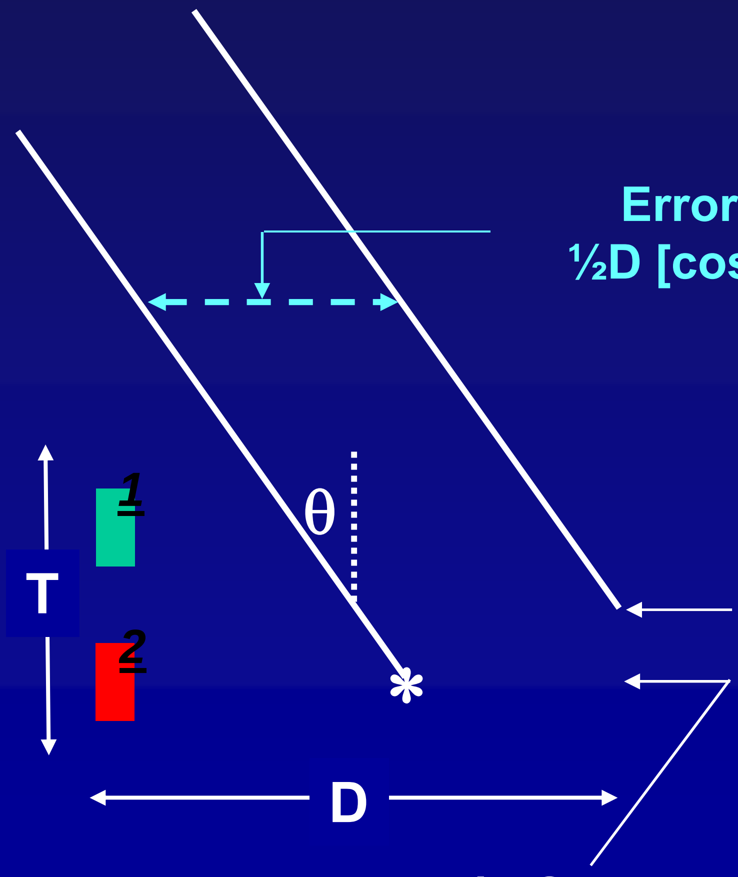
Depth-of-Interaction (DOI) Effect

(Partial) Recovery of "30%" Degraded Resolution:

Phoswich Detectors

Bi-layer detector comprised of 2 scintillators with different τs

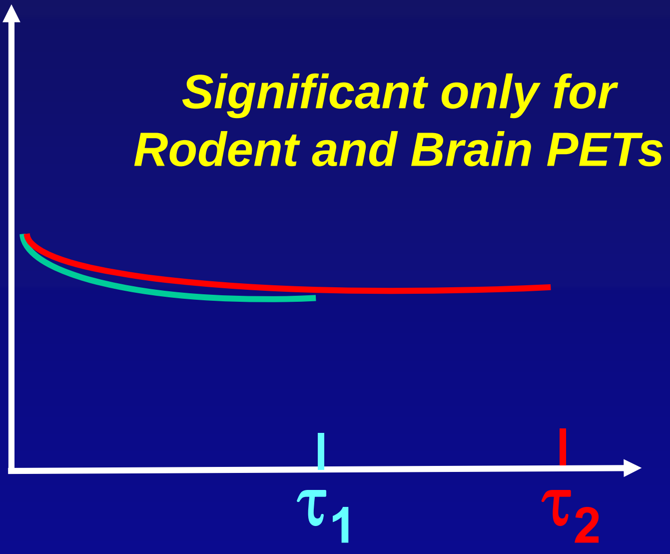
eg **LSO and LYSO**



Error in LOR path ≈ $\frac{1}{2}D\,[\cos\theta + (D/T)\sin\theta]$

Assumed **DOI:**
Mid-depth
of total thickness
of single-material
detector

Actual **DOI**



Significant only for Rodent and Brain PETs

Light decay time = τ_1, interaction in 1
Light decay time = τ_2, interaction in 2

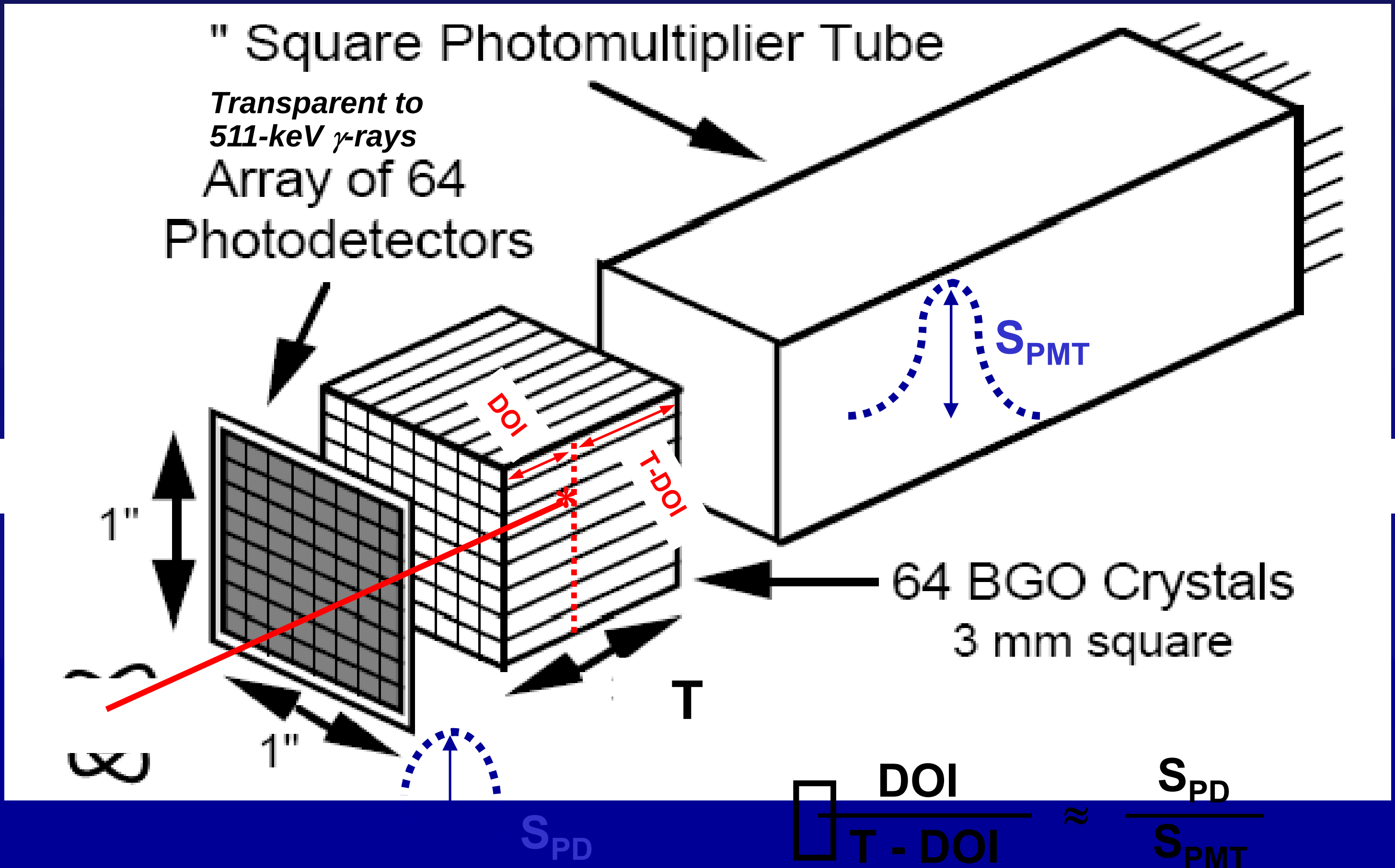
LOR path error reduced by ~50%

Depth-of-Interaction (DOI) Effect

Recovery of “30%” Degraded Resolution:

Photodetector-based DOI-Measuring Module

Increases cost of detector module by ~25% (or $200)



$$\frac{DOI}{T - DOI} \approx \frac{S_{PD}}{S_{PMT}}$$

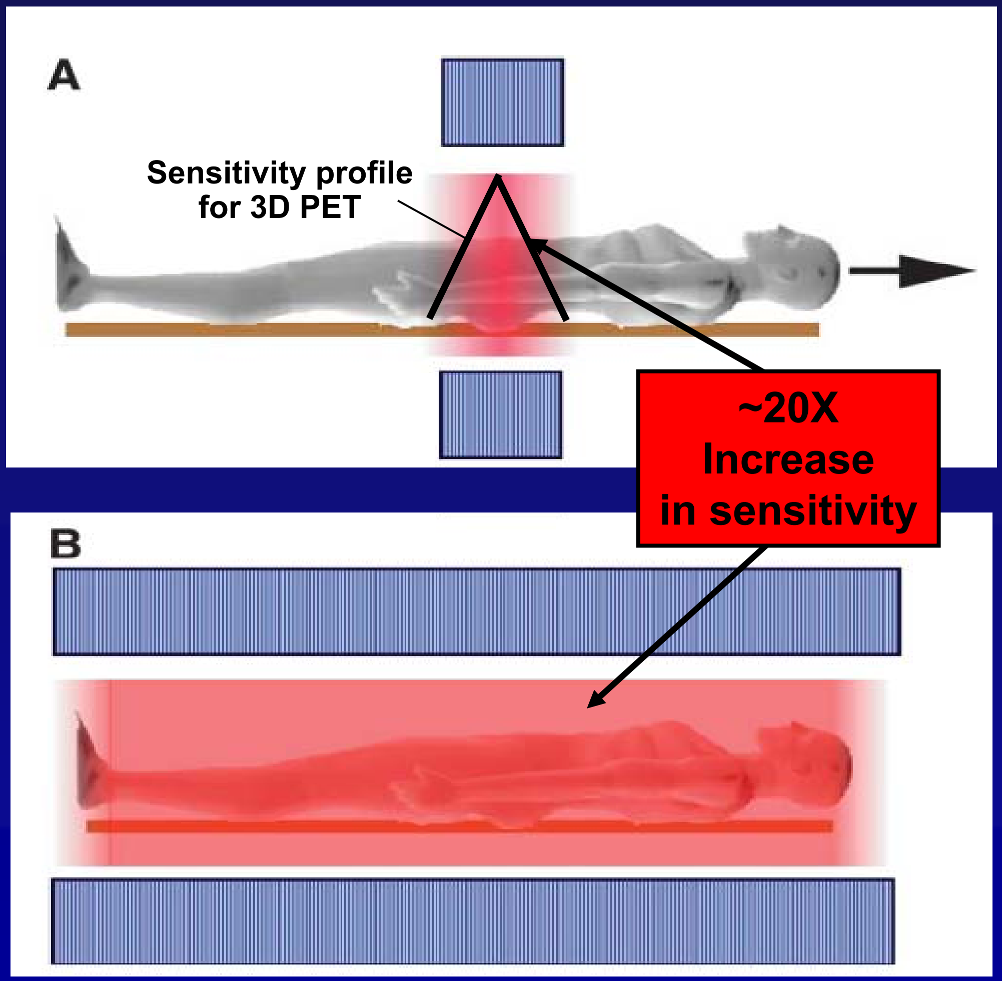
Whole-body PET Scanning? *

~~PET w/ Ge68 AC~~

~~Acquire data spanning 15-25 cm of the body at each of 6-8 bed positions for: ~9 min each – emission data (~6 min) and transmission data (~3 min) for AC → ~1 hr per patient~~

PET-CT

Acquire data spanning 15-25 cm of the body at each of 6-8 bed positions for: ~6 min each – emission data (~4 min) plus whole-body CT (~2 min total) for AC → ~1/2 hr per patient



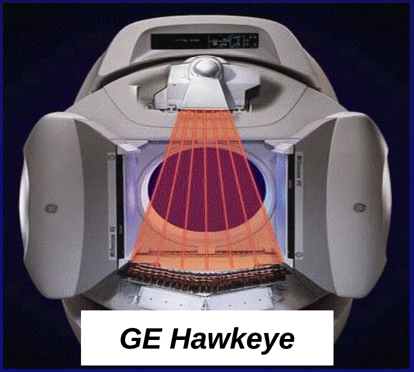
* "Whole-Body" PET? 50 to 70 cm longitudinal FOV scanners under development
Large-panel detectors - Otherwise cost-prohibitive (>$10M)?

Multi-Modality Devices *

"Intrinsic" image registration:
Fixed rigid transform between modalities

Clinical

SPECT-CT



GE Hawkeye

Siemens Symbia

Philips Precedence

PET-CT

Siemens-CTI Biograph

GE Discovery

Phillips Gemini

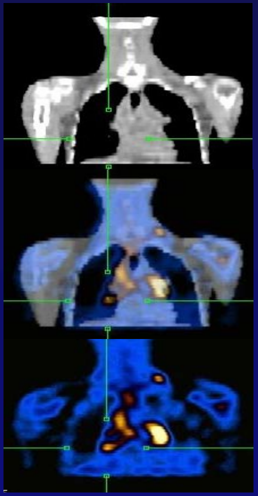
Small-Animal

X-SPECT + X-O

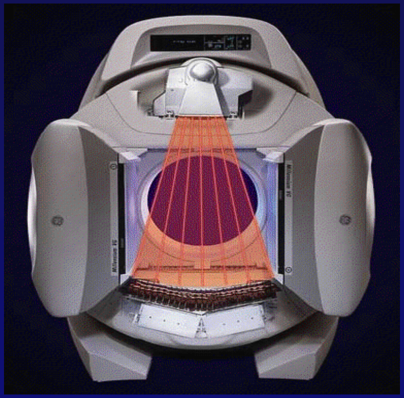
Gamma Medica
X-SPECT +/-
X-PET +/-
X-O

* ***Additional application***
CT-based attenuation correction

SPECT-CT and PET-CT
A Continuing Evolution

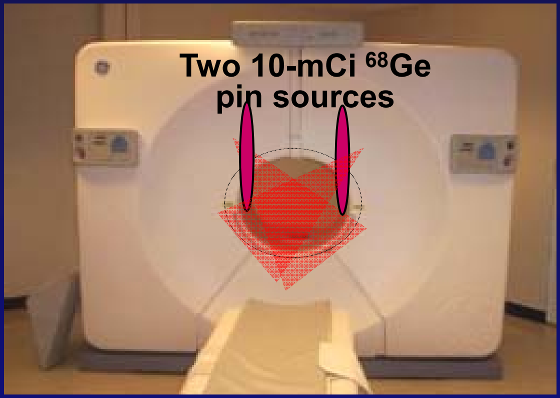


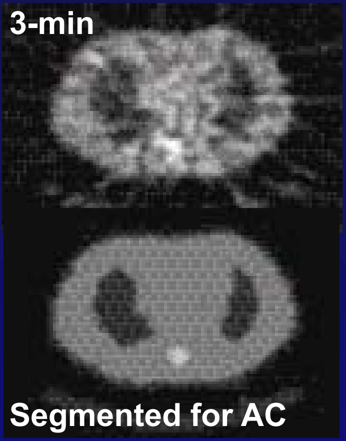
SPECT



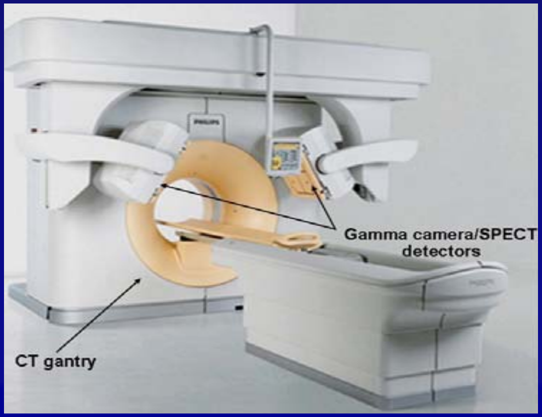
AC,
Anatomy
Lo Dose

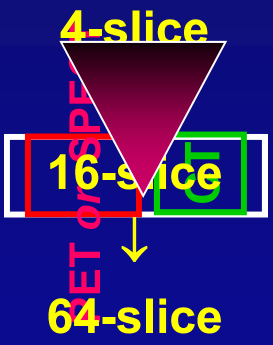
PET

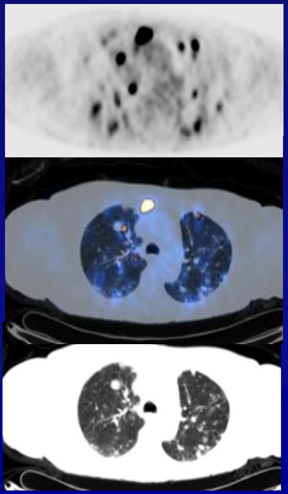




Lower mAs
Lower kVp
Higher pitch







Higher mAs
Higher kVp
Lower pitch
± Contrast

PET-CT (spiral) Scanners

3D / LSO

FWHM = 5 mm
τ = 40 nsec
ε = 250 cps/μCi

Siemens-CTI Biograph PET-CT

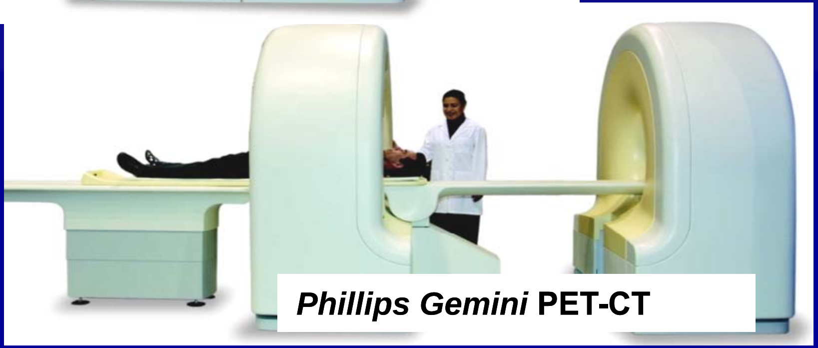
3D or 2D / BGO

FWHM = 5 mm
τ = 300 nsec
ε = 250 cps/μCi

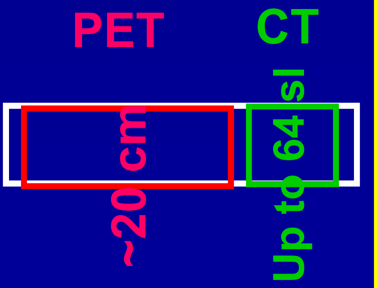
GE Discovery PET-CT

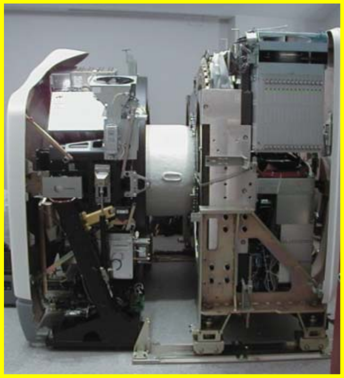
3D / GSO

FWHM = 5 mm
τ = 60 nsec
ε = 500 cps/μCi



Phillips Gemini PET-CT





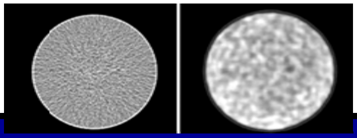
Dose Reduction Strategies in PET-CT

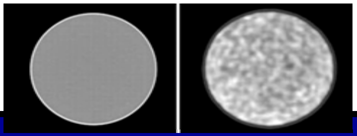
Effect of CT Protocol on Dose

	Dose *(rem)*				
	^{18}FDG *10 mCi*	PET w/ ^{68}Ge Transmission Scan *	PET-CT w/ "Low-Dose" CT *	PET-CT w/ "High-Quality" CT *	PET-CT w/ "Diagnostic" CT *
			Attenuatio Correction	Anatomic Registration	Diagnosis
Bladder *	4.4	4.4	4.4	4.9	6.8
Bone Marrow	0.48	0.49	0.53	0.90	2.3
Breasts	0.34	0.35	0.38	0.69	1.8
Liver	0.58	0.60	0.66	1.2	3.2
Lungs	0.64	0.66	0.70	1.1	2.5
Ovaries	0.48	0.51	0.54	1.0	2.4
Effective Dose	1.1 **	1.1	1.2	1.7	3.3
Transmission Scan Contribution		*3%*	*9%*	*41%*	*71%*
		kVp	120	120	140
		mAs	10	60	190
		Pitch	1.5	1.5	1.25

* 3-hr voiding interval

** Effective dose equivalent





Adapted from NUREG/CR-6345 1996.
Groves *et al.* Br J Radiol 77: 662, 2004.
Huda & Vance. AJR 188: 540, 2007.
Fahey. Radiology on-line/pre-print, 2007.

* No difference in SUV

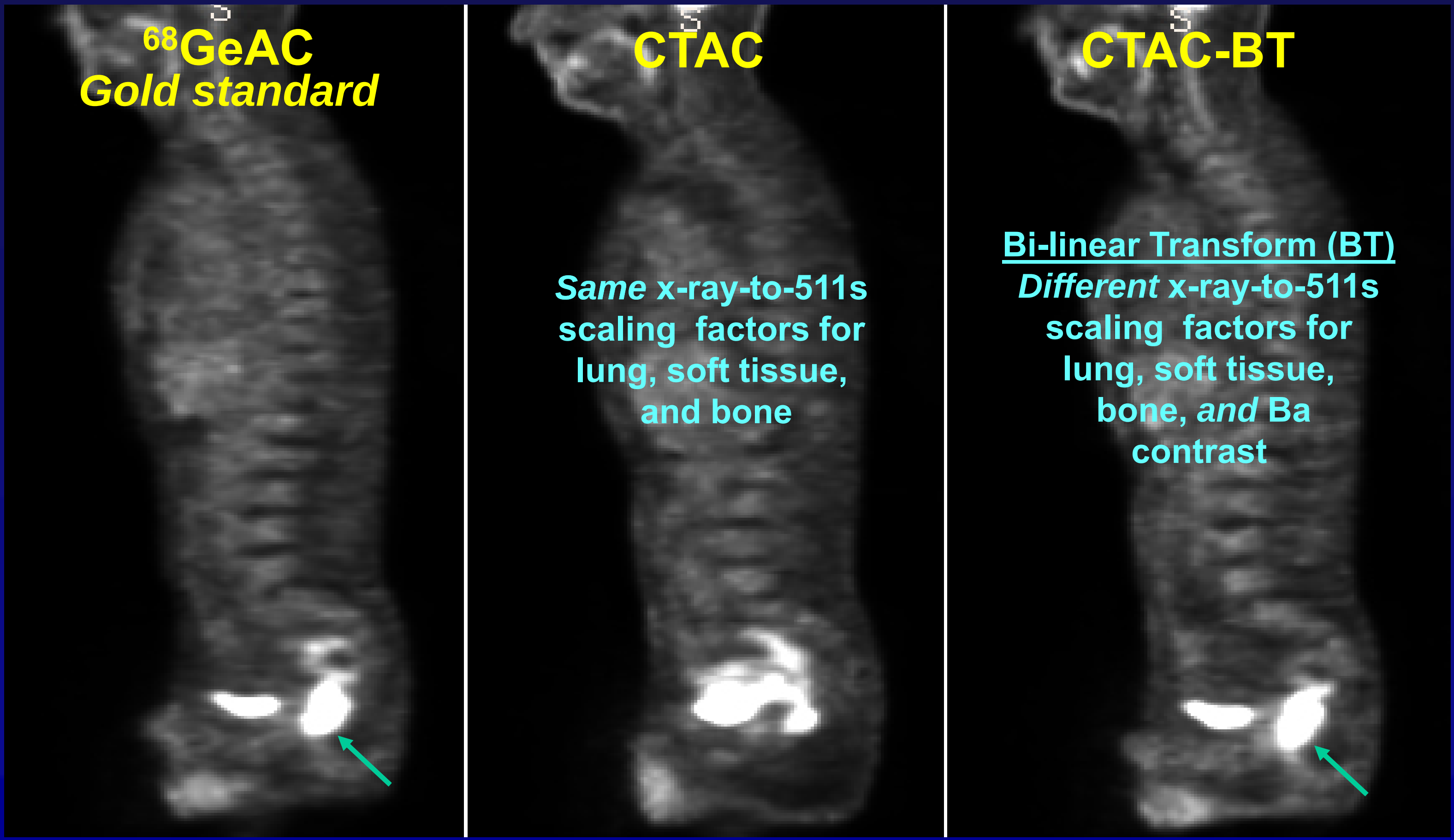
Kamel *et al.* Eur J Nucl Med 29: 346, 2002.

PET-CT

Contrast Artifacts in CT Attenuation-Corrected PET Images

FDG-PET/CT Scan

45-yr-old man w/ rectal carcinoma
RT planning sim CT w/ 240 ml diluted $BaSO_4$ (50%) and 15 ml concentrated $BaSO_4$ + 15 ml of air in enema



^{68}GeAC
Gold standard

CTAC

Same x-ray-to-511s scaling factors for lung, soft tissue, and bone

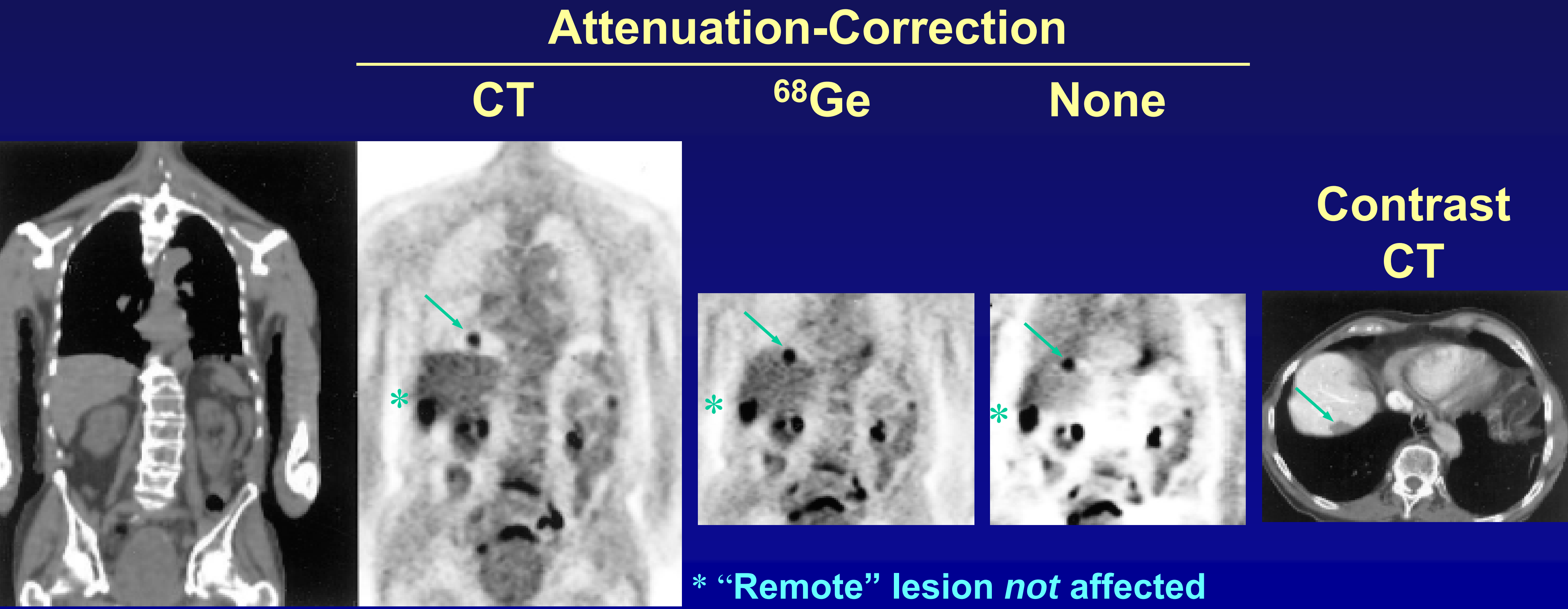
CTAC-BT

Bi-linear Transform (BT)
Different x-ray-to-511s scaling factors for lung, soft tissue, bone, *and* Ba contrast

Nehmeh, Erdi *et al*.
J Nucl Med 44: 1940, 2003

	SUV$_{max}$		
Lesion	14	15 (+9%)	13 (-1%)
Bladder	36	59 (+62%)	37 (+1%)
Bowel	6.7	11 (+66%)	6.3 (-5%)

PET-CT
Lesion Misplacement Due to Respiration



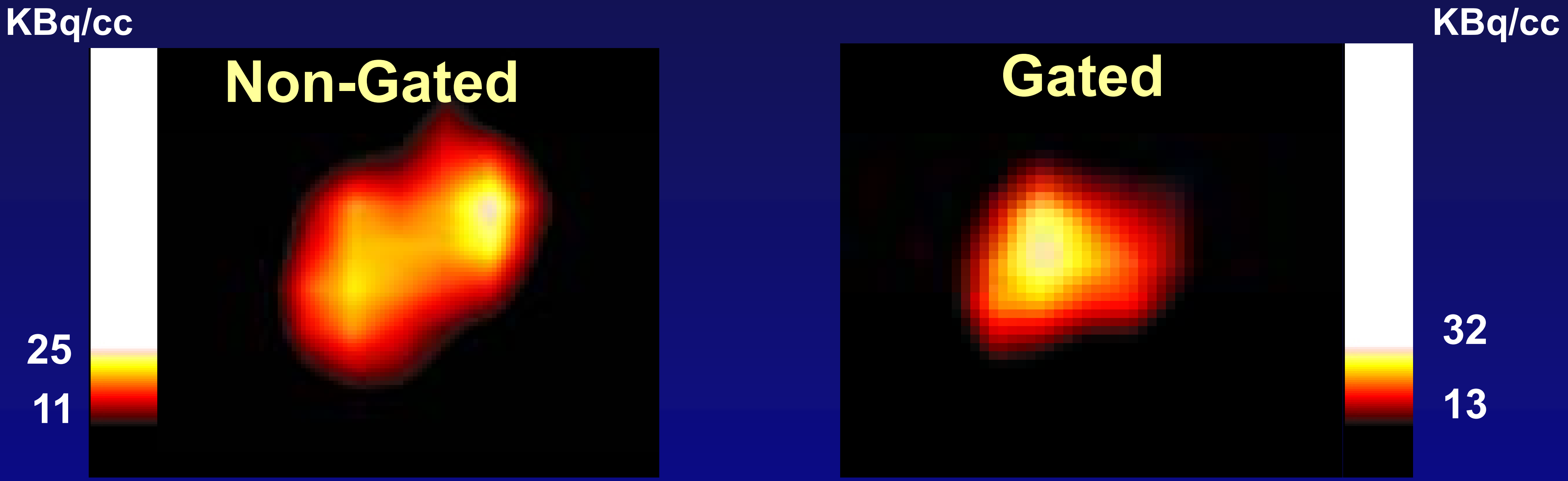
* “Remote” lesion *not* affected

- 81-year-old man w/ rising CEA dx’d 5 yr earlier w/ colorectal ca
- 12 mCi FDG, 60-min pi images, GE Discovery LS PET-CT

Sarikaya, Yeung, Erdi, and Larson. Clin Nucl Med 28: 943-944, 2003

Non-Gated *vs* Gated PET

Improved Lesion Sizing and Activity Quantitation



35% *

Area = 4.2 cm^2 ⟷ Area = 2.7 cm^2

31% *

SUV$_{max}$ = 8.7 ⟷ SUV$_{max}$ = 11

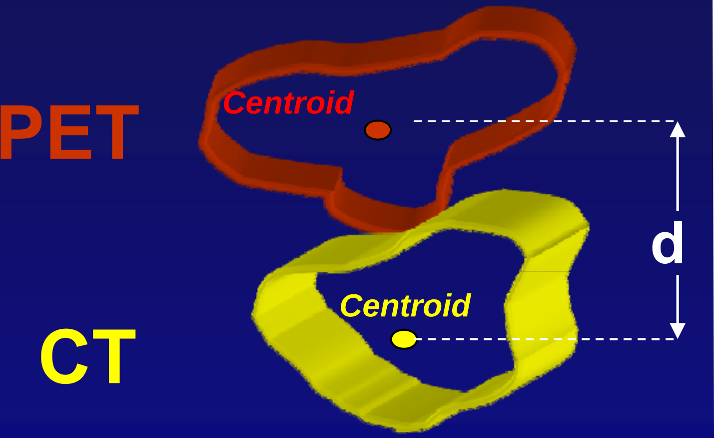
** In 5-patient pilot study:* 14-35% DECREASE in Nodule Volume
8-160% INCREASE in SUV$_{max}$

Nehmeh, Erdi *et al*. J Nucl Med 44: 1644, 2003 and J Nucl Med 45: 1287, 2004.

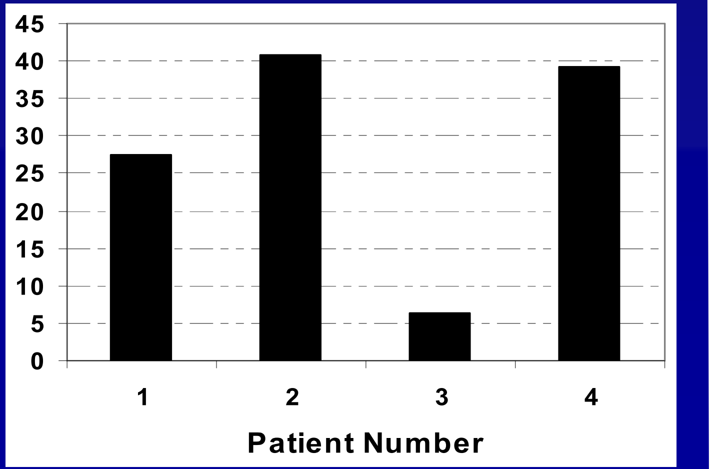
4D-PET/CT

= *Gated* PET + *Retrospectively* Re-binned (Gated) CT

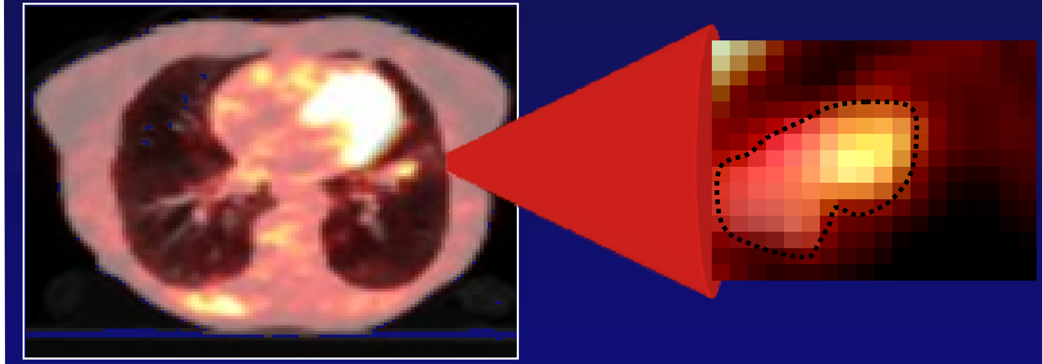
Improved “Local Co-Registration,” Image Quality, and Quantitative Accuracy



% Difference in d: Clinical - Gated PET/CT



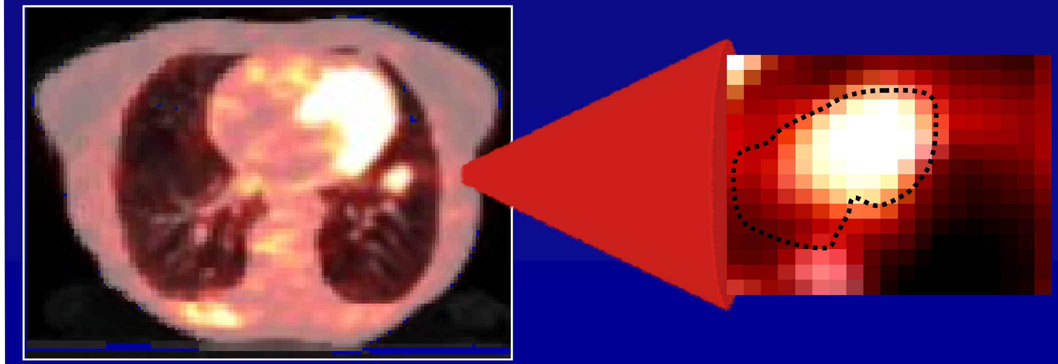
1	27.5
2	41
3	6.5
4	39



SUV_{max} = 3.3

Gated-PET w/ Helical CTAC

34% *



SUV_{max} = 4.4

Gated-PET w/ 4D CTAC

* *In 4-patient* 5-19% DECREASE in Volume <u>Difference</u>
pilot study: 7-37% INCREASE in SUV_{max}

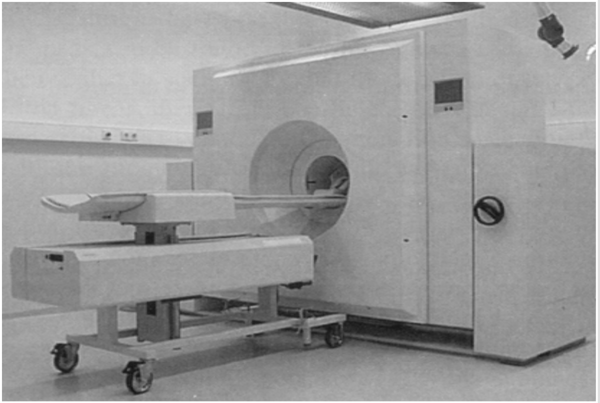
Nehmeh, Erdi *et al*. Med Phys.

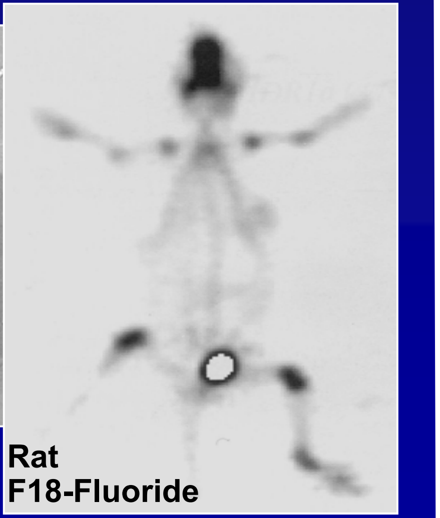
Large-Panel *(Lower-Cost)* Detectors *Re-visited*

Not being pursued commercially

High-resolution Research Tomograph HRRT (Siemens-CTI prototype)

- 8 15x22 cm flat-panel detectors
- Opposed detectors 47 cm apart
- 9x13 7.5-mm thick LSO blocks cut into 2x2-mm crystals
- Resolution: ~3 mm
- Sensitivity: ~350 cps/μCi
- Brain and small-animal imaging





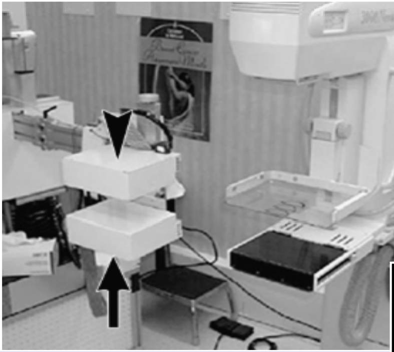
Rat
F18-Fluoride

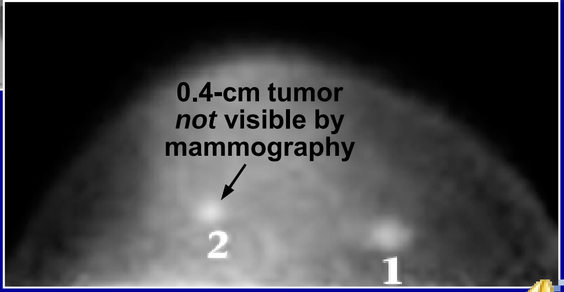
Boellard *et al*. Phys Med Biol 48: 429, 2003

Full ring-detector Mammo PET/CT being developed by Cherry

Mammo-PET

- 2 opposed 15x20 cm flat-panel detectors
- 10-mm thick LSO blocks cut into 3x3-mm crystals
- 6-9 cm apart (compression)
- Adaptable to biopsy table





1.5 mCi FDG
5-min image

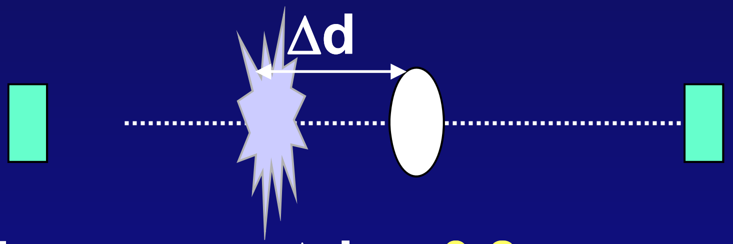
Rosen *et al*. Radiology 234: 527, 2005

Time-of-Flight (TOF) PET

Re-visited

Determine <u>location between two detectors</u> at which annihilation occurred by determining the difference in time Δt at which the annihilation photons are detected

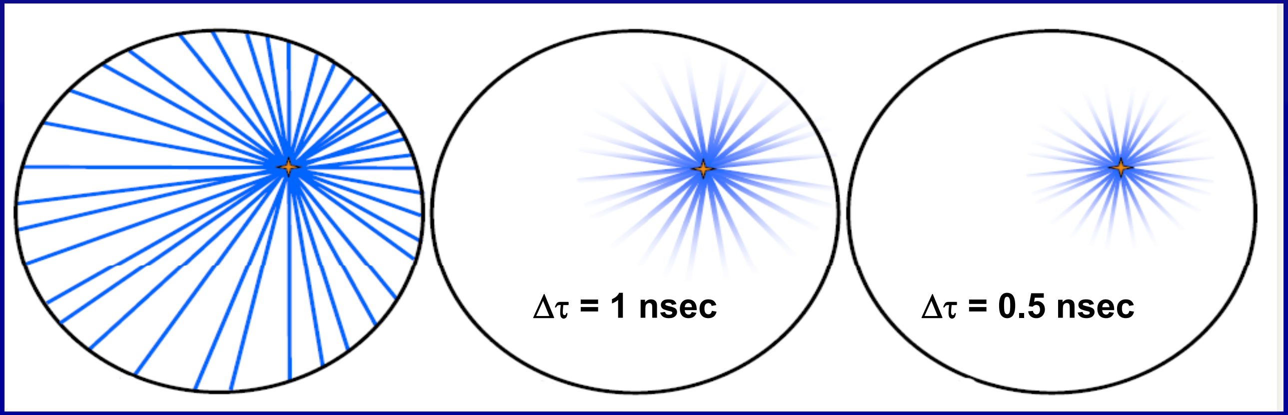
$$\Delta d = \frac{\Delta\tau \bullet c}{2}$$



$\Delta\tau = 50$ psec = 0.05 nsec → Δd = **0.8 cm**

$\Delta\tau = 500$ psec = 0.5 nsec → Δd = **8 cm**

Conventional *TOF*

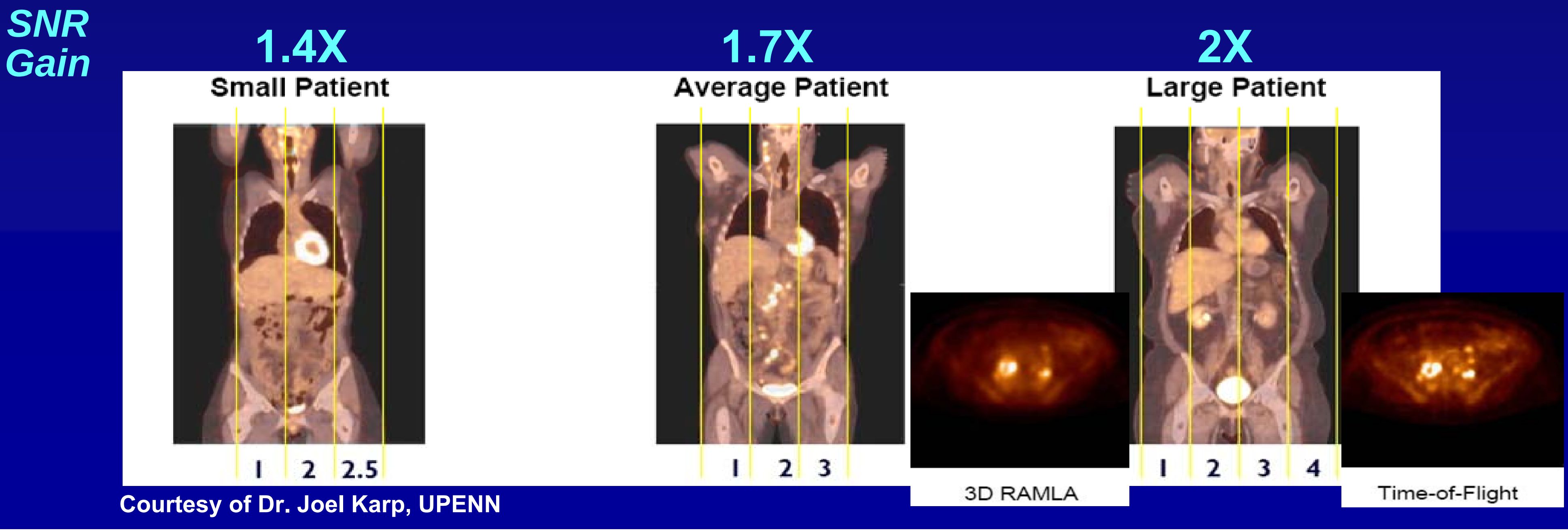


Randoms over most of source are eliminated

Time-of-Flight (TOF) PET
Re-visited

TOF PET does *not* improve spatial resolution but does reduce the randoms count rate - by ~50% @ 1-nsec timing resolution - and the reduction is greater for larger sources (ie larger patients)

$$SNR_{TOF} \approx \sqrt{\frac{2D}{c\,\Delta\tau}}\; SNR_{non\text{-}TOF}$$



Courtesy of Dr. Joel Karp, UPENN

1st Current-Generation Commercial Time-of-Flight (TOF) PET

Philips Gemini TF

PET scanner

LYSO : 4 x 4 x 22 mm^3

28,338 crystals, 420 PMTs

70-cm bore, 18-cm axial FOV

CT scanner

Brilliance 16-slice

Installation at U.Penn Nov ’05

Validation and research patient imaging

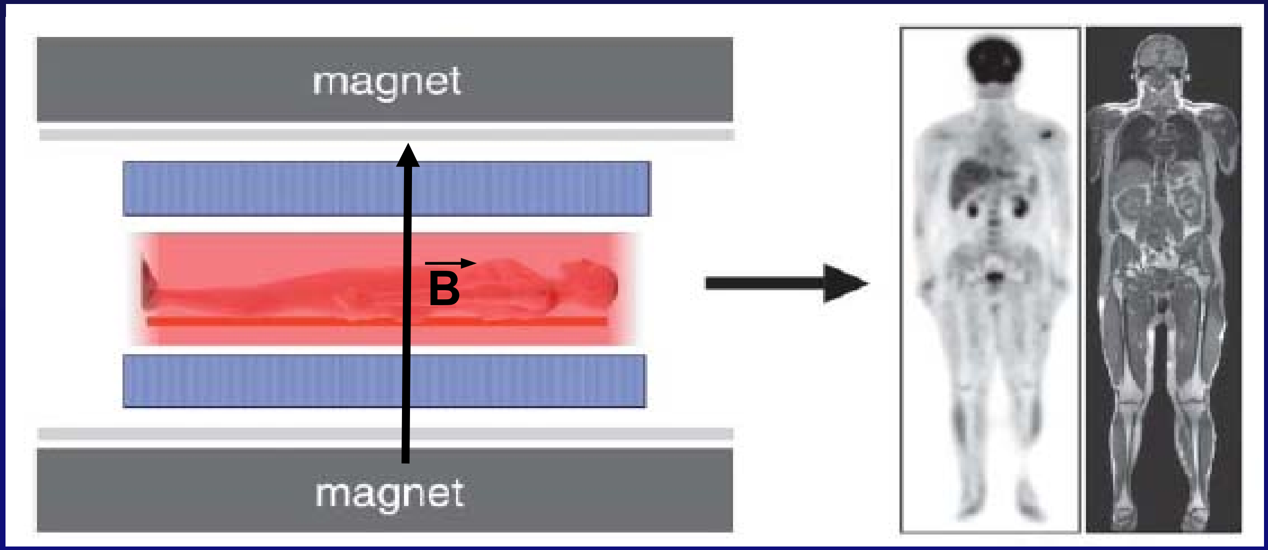
Nov ’05 - Apr ’06 *50 patients*

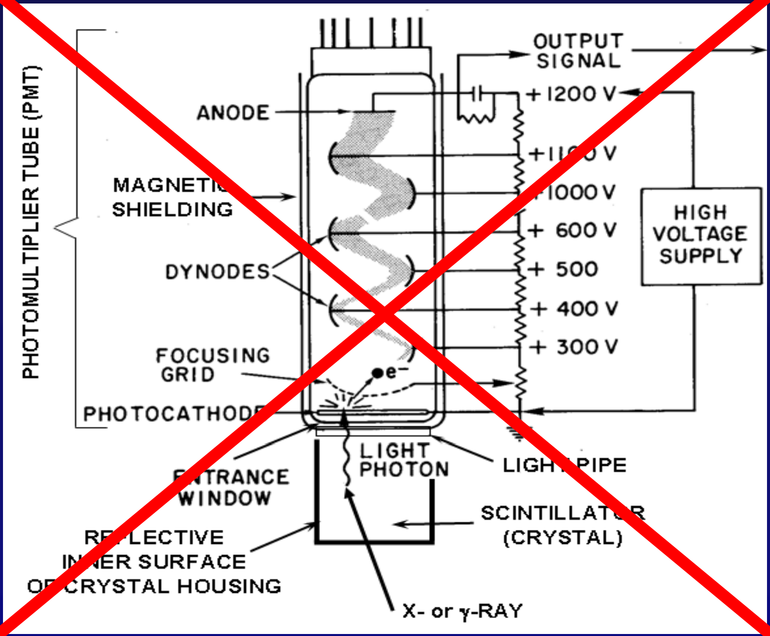
Beta testing and upgrade to production release software

May ’06 - Jun ’06 *40 patients (to date)*

Timing resolution = 600 ps

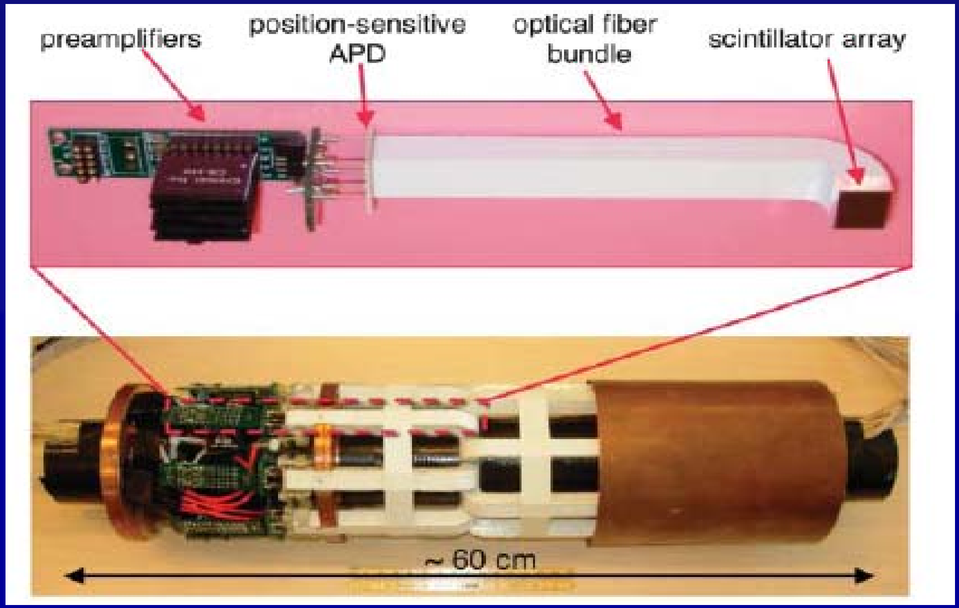
PET-MRI



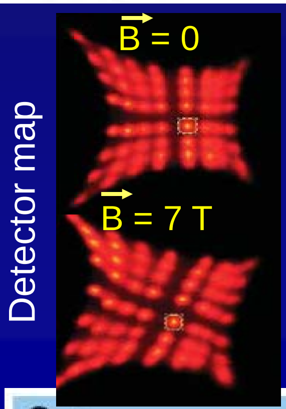


Conventional PMT-based Scintillation Detectors

e^- trajectory perturbed by $\vec{B}$



Cherry. JNM 47: 1735, 2006



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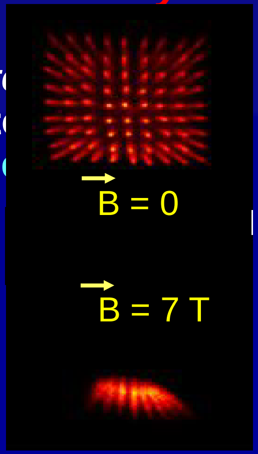
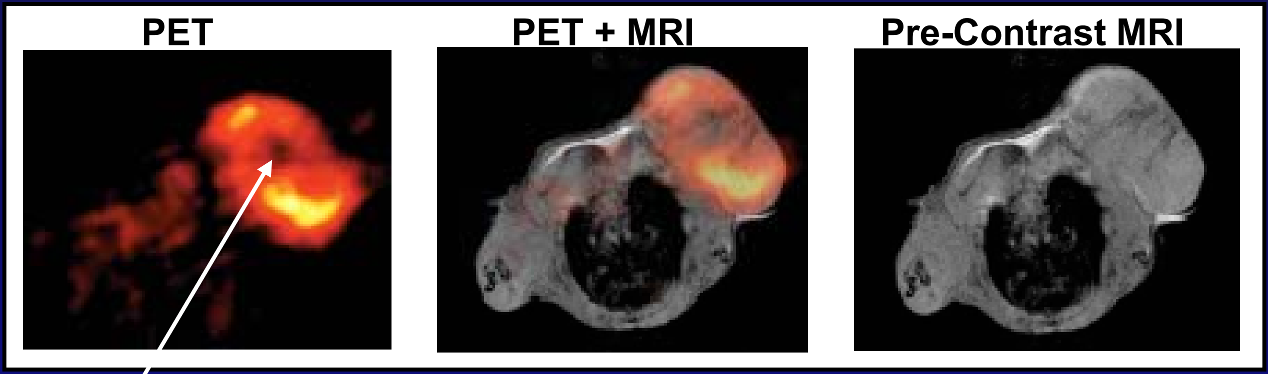
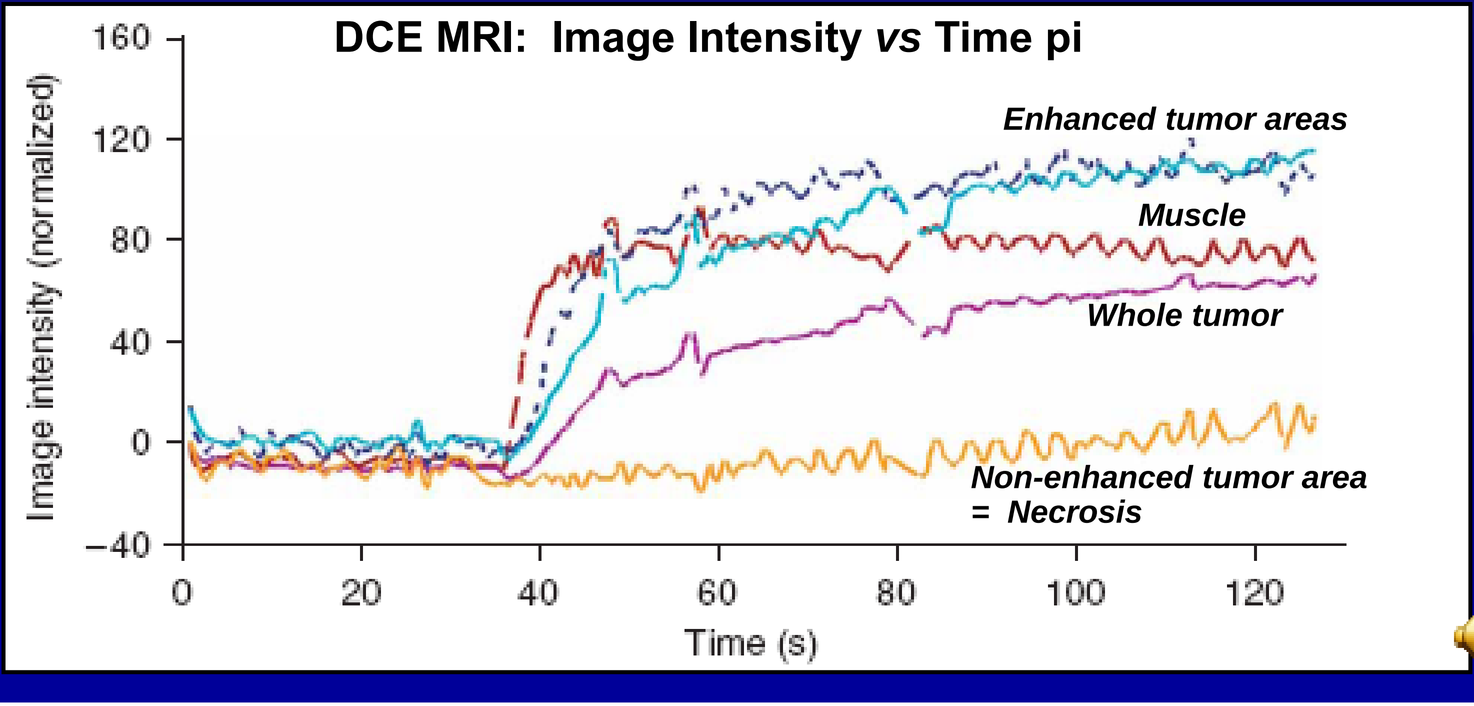


PET-MRI *cont*

F18-FLT PET + Pre- and Post-Contrast T1-weighted MRI
Balb/C mouse w/ a CT26 colon carcinoma xenograft in the shoulder

PET and MRI are truly simultaneous





Judenhofer *et al*.
Nature Med 2008

Future of PET

- Detectors
  - Fast - Ceramic and other inorganic scintillators
  - Higher quantum efficiency - APDs
- Extended axial FOV
- Depth-of-Interaction Correction
  - For small-animal, brain, breast PETs

Thank You!

- New reconstruction algorithms (3D)
- Respiratory-gated PET & PET-CT (4D PET-CT)
- TOF PET
- PET-MRI