PACE Seminar, 4/20/2020

PET Quantitation and Quality Control

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Qualitative vs. Quantitative Analysis

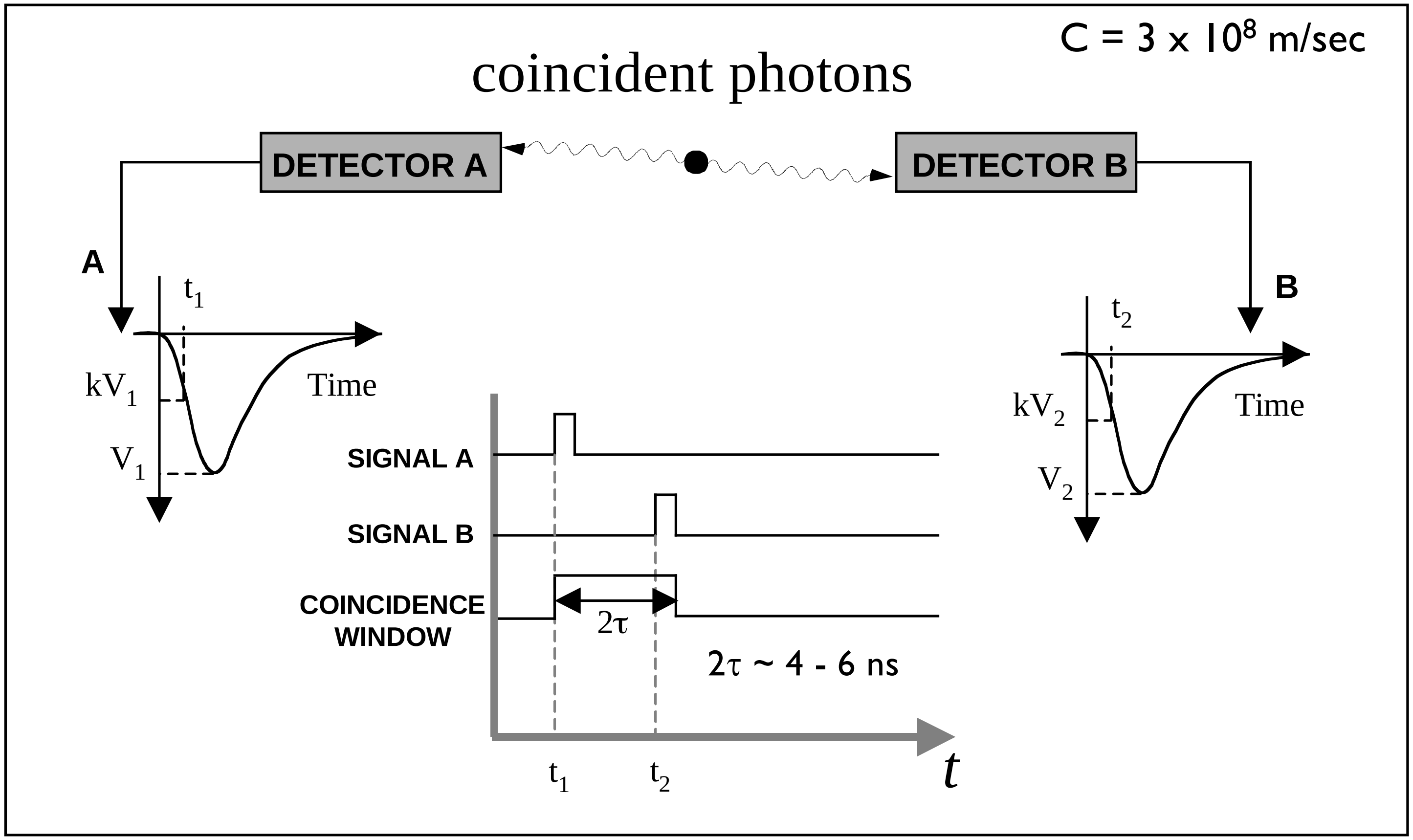
Visual assessment may be adequate for diagnosis and staging but:

- Quantitative measurements provide objective, more accurate, less observer-dependent measures
- Quantitative accuracy and precision particularly important when pooling data from multiple patients/equipment/sites in clinical trials
- Difficult to achieve
- To extent that CAN achieve quantitative accuracy and precision, benefits include:
  - Earlier stratification of responders / non-responders
  - Reduce the sample size necessary to achieve statistical and clinical significance

How to achieve accurate quantification?

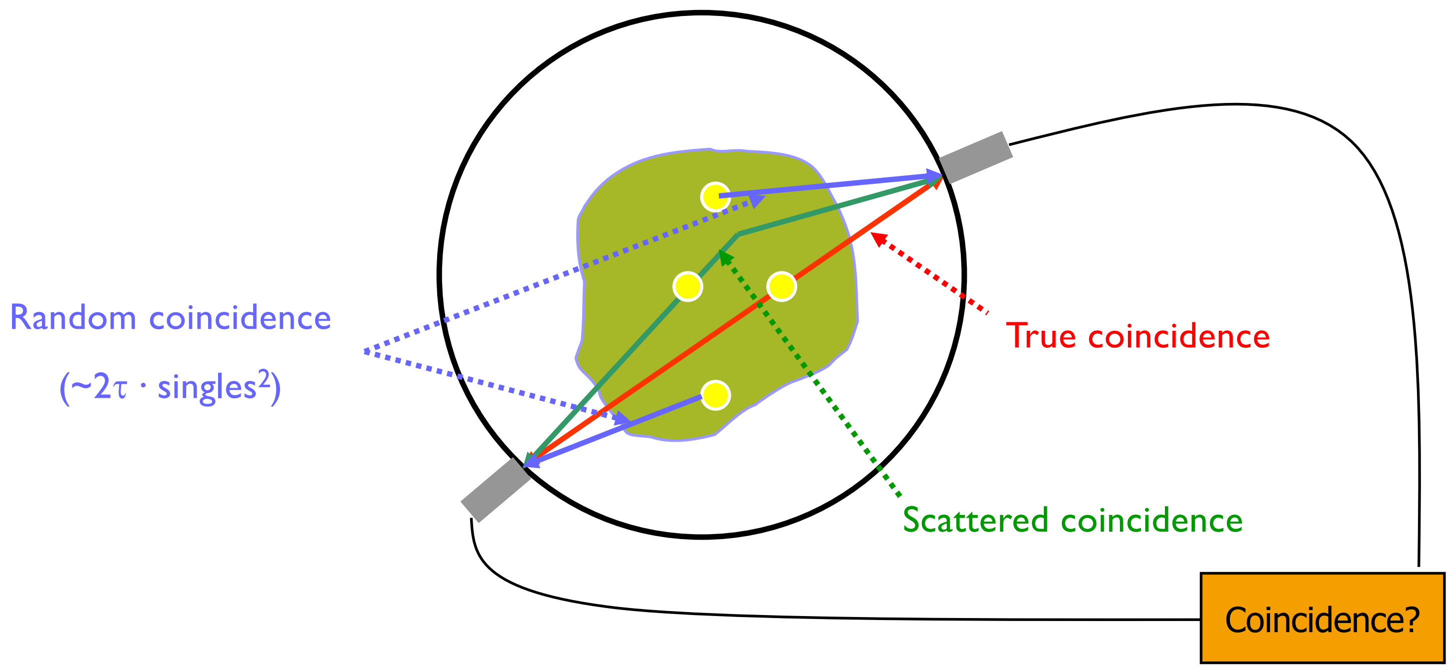
- Goal is that after image reconstruction, the voxel intensity in the image will be directly proportional to the amount of radioactivity at the corresponding location in the patient.
- Necessary to
  - Develop a set of corrections that accurately compensates for imperfections in the detection system like nonlinearities, nonuniformities, etc.
  - Develop corrections to account for effects in the patient, like scattered and attenuated photons

Coincidence Detection

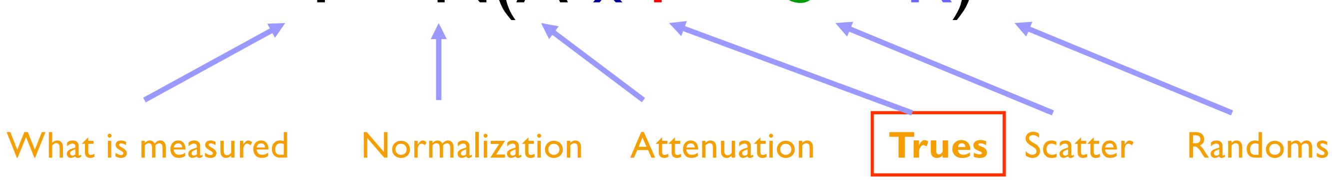


Timing coincidence window must be long enough to account for 1) time for photon to cross transaxial FOV to reach detectors, and 2) differences in signal transit time through cables and electronics.

What is Actually Measured with PET scanner



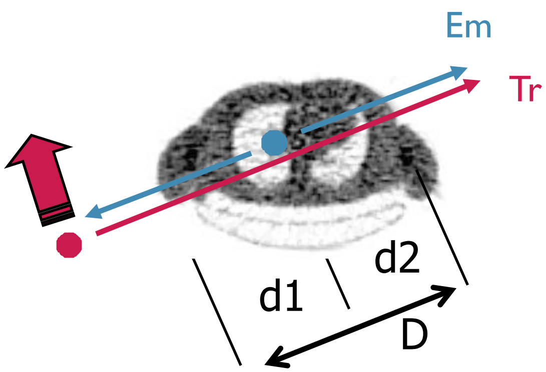
$$Y = N(A \times T + S + R)$$



Corrections needed for Quantification

- Attenuation Correction
- Scatter Correction
- Randoms Correction
- Dose Calibrator Cross-Calibration
- Linearity / Distortion Correction
- Energy Correction
- Normalization
- Deadtime Correction

Attenuation Correction



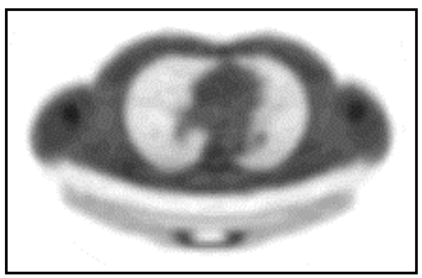
Emission

$$I / I_0 = e^{-\mu d1} \cdot e^{-\mu d2} = e^{-\mu D}$$

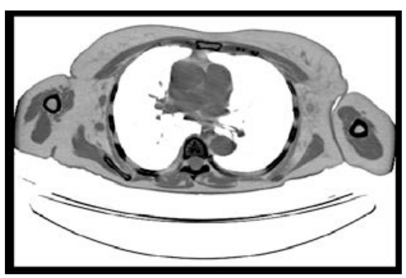
Transmission

$$I / I_0 = e^{-\mu D} \text{, therefore } AC = e^{\mu D}$$

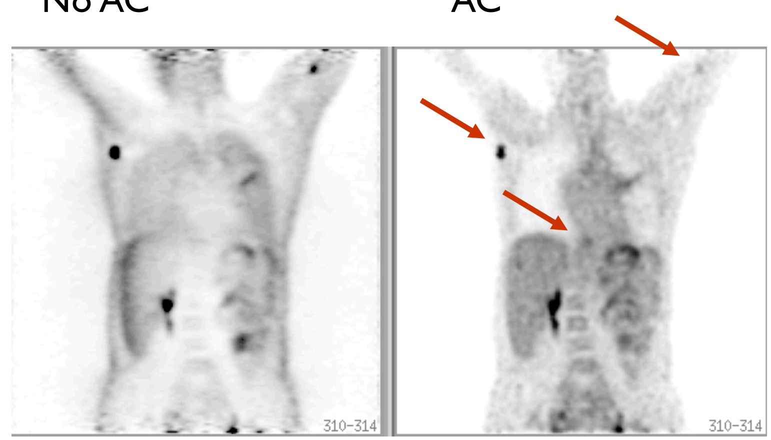
Single photon ^{137}Cs (662 keV)



X-ray CT (~30-140kVp)

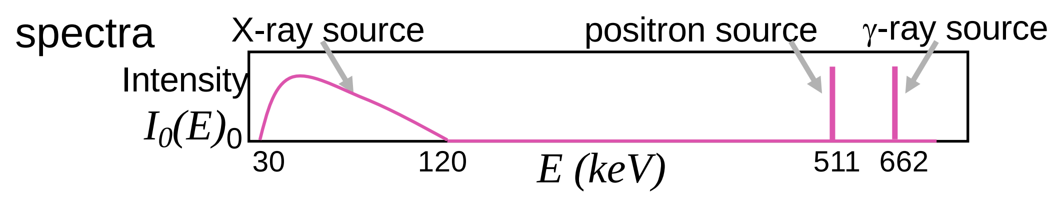


No AC AC



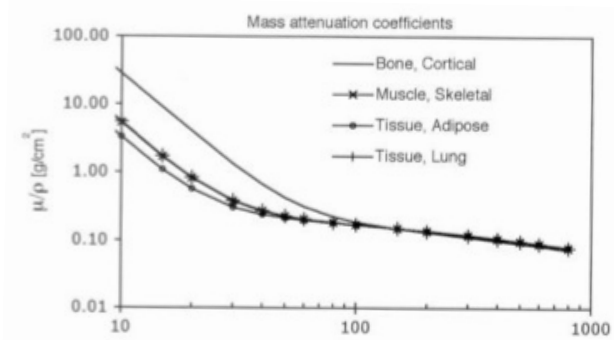
X-ray CT has replaced gamma-ray transmission sources for attenuation measurements

X-ray CT scan - source of X-rays with energies from ~30 to 120 keV. We assume an ‘effective’ energy of ~ 75-80 keV

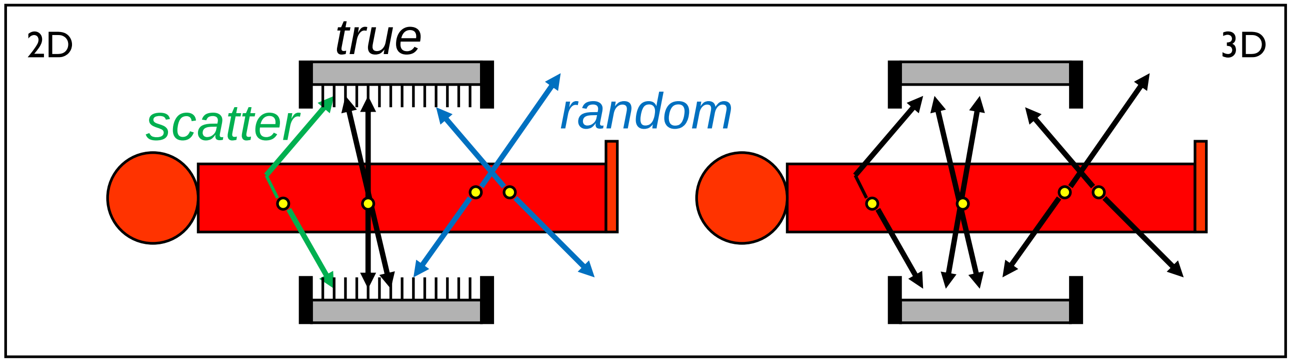


(Recall that the PET emission data is attenuated at 511 keV)

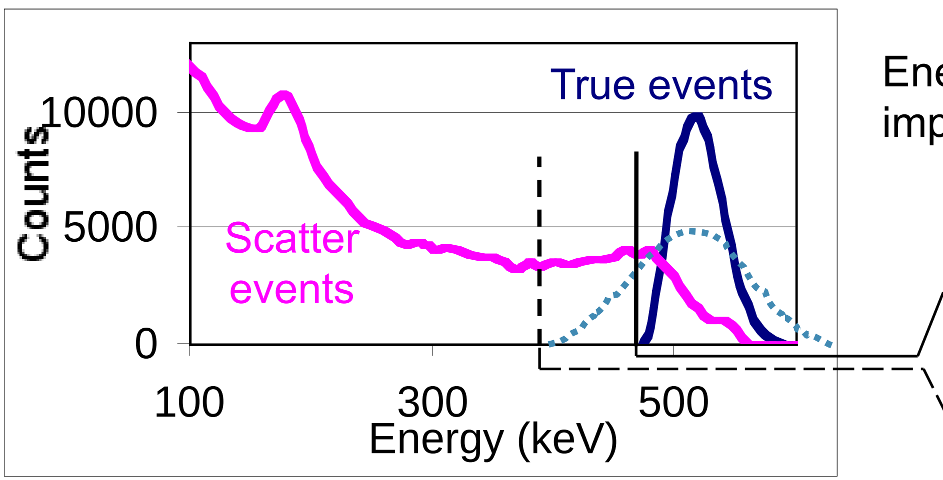
To create map of attenuation coefficients from the CT need to down-sample images to match PET resolution, then scale the measured values to account for energy difference between X-rays and positron annihilation photons



3D Imaging: higher sensitivity than 2D but increased scatter



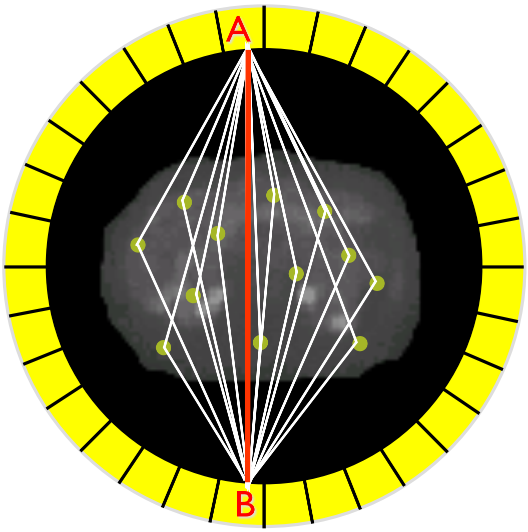
2D septa allow mechanical rejection of scatter, randoms



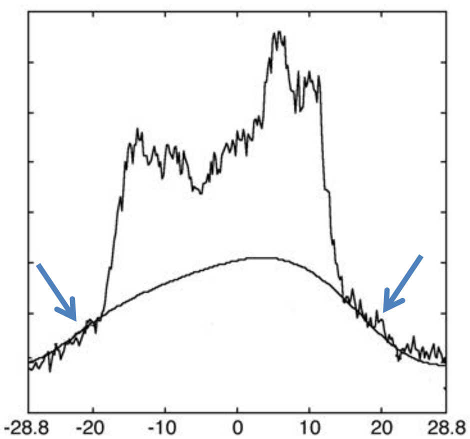
Energy rejection important for 3D

threshold with good energy resolution -> less scatter events

threshold with poor energy resolution -> more scatter events



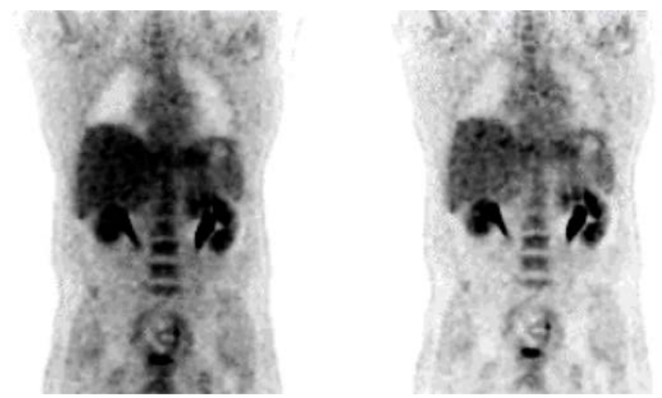
Scatter Correction



Single Scatter Simulation*

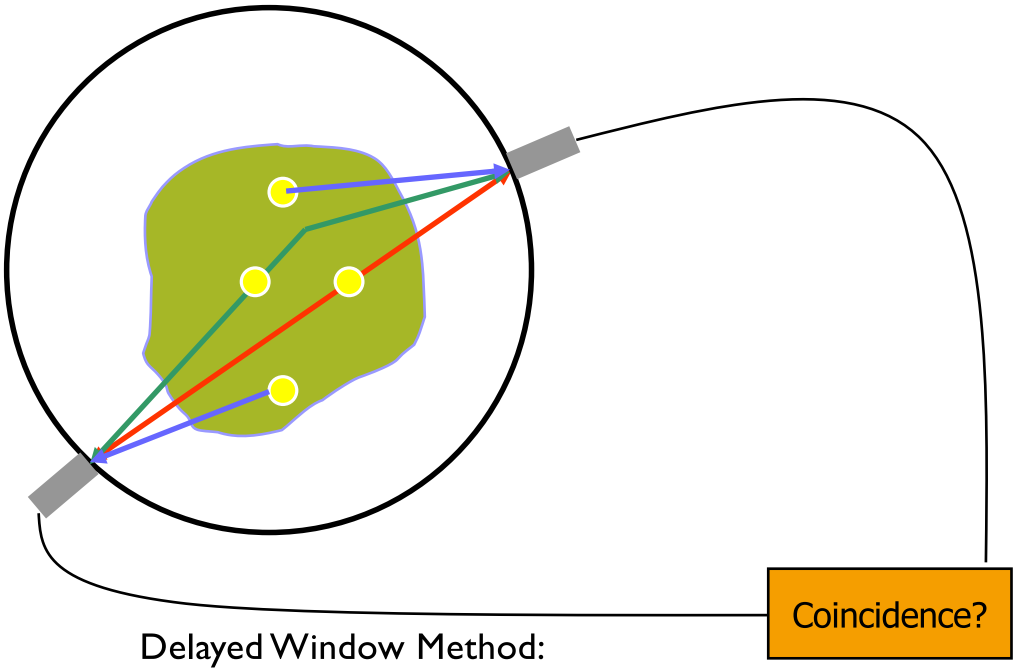
- Calculate the contribution for an arbitrary scatter point using the Klein-Nishina equation and solid angles
- Scaling of result is required to compensate for multiple scatter and other factors

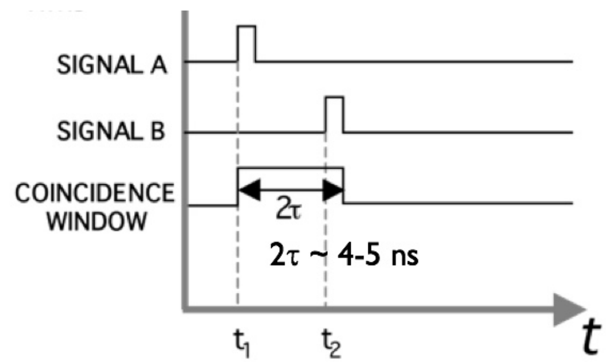
- Tail fitting <u>slice-weighted </u>scaling
  - Scale the SSS scatter estimate by matching the counts in the LORs outside the body.
- Scaling factor derived from Monte Carlo simulation



*C. Watson, "Extension of single scatter simulation to scatter correction of time-of-flight PET," IEEE Transactions on Nuclear Science, vol. 54, no. 5, pp. 1679-1686, 200

Randoms Correction





Delayed Window Method:

- Collect another set of data where introduce a delay in the coincidence timing window by a time much greater than its width
- So, for example, instead of looking from in first 5-6 ns for a coincidence, look from 60 to 66 ns for a coincidence. There can be no true events there, so an event identified as being a coincidence must be due to randoms. Sort these events into a sinogram and smooth it and apply during reconstruction.

Dose Calibrator Cross-Calibration

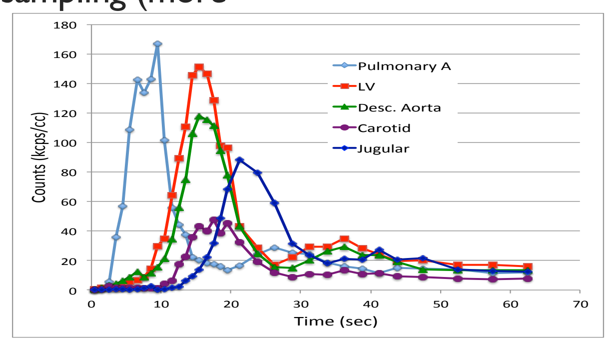
- Absolute quantification of measured activity concentration in a reconstructed image.
- A dose is measured in the dose calibrator (~2 mCi) used to measure patient doses.
- The dose is injected into a uniform cylindrical phantom of known volume, usually between 5.6 and 9.3 liters.
- Phantom is well mixed to ensure uniform concentration throughout.
- Phantom is scanned on PET scanner using standard patient protocol and average concentration measured in reconstructed image.

Range of image interpretation

Degree of difficulty

Ability to make absolute measurements

- Visual analysis (qualitative imaging)
- Semiquantitative analysis based on Static Imaging/Wholebody Imaging
  - Most common metric: Standardized Uptake Value (SUV)
  - Provides a snapshot of a dynamic process
- Kinetic analysis (considered the gold standard)
  - Applying a pharmacokinetic model to data derived from dynamic PET studies
    - Until recently could cover only one bed position (18 – 26 cm)
    - Requires longer scan (60 - 90 min)
  - Measuring input function may require arterial blood sampling (more technically demanding)
  - Provides measurement of rate of process



PET Scan Quantitation
Standardized Uptake Value (SUV)

- What is it?

SUV = (Activity Concentration in region) / (Activity Concentration in whole volume)

$$SUV_{ROI} = \frac{A_{ROI}(T_S)}{Conc_S(T_S)}$$

Conc = Dose/Weight
T_s is time of scan

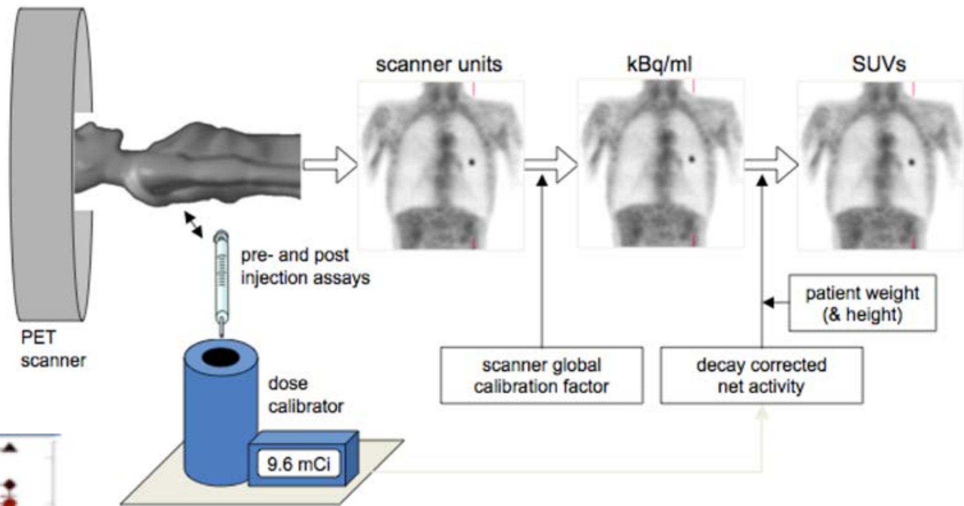
$A_{LESION}(T_S)$ = 7.8 kBq/mL
SUV_{LESION} = 1.8

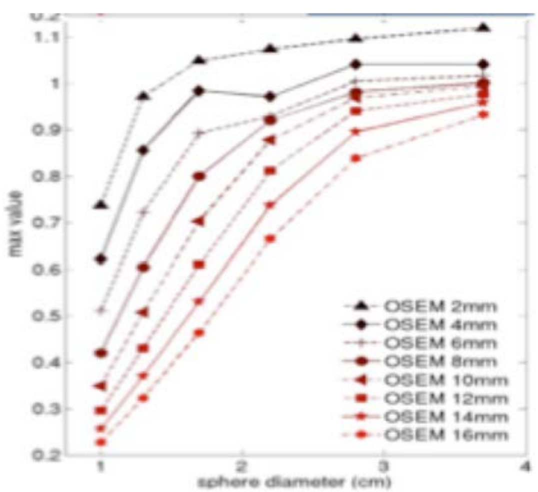
Common Sources of Errors in SUV calculation

- Incorrect patient weight (which is used as surrogate for distribution volume)
  - Failed to weigh patient
  - Typed the number in incorrectly
  - Faulty lbs to kg conversion
- Improperly synchronized clocks – dose calibrator and scanner clocks differ
- Incorrect measurement of dose or residual (wrong amount or time), incorrect calculation of net activity injected, mistake in data entry

Chain of data quantitation

Accuracy depends on many factors: dose assay, instrument calibration, reconstruction





SUV depends on lesion size and image reconstruction parameters

Further reading about factors affecting quantification in FDG PET

- Extensive literature on this topic with a multitude of recommendations and procedure guidelines:

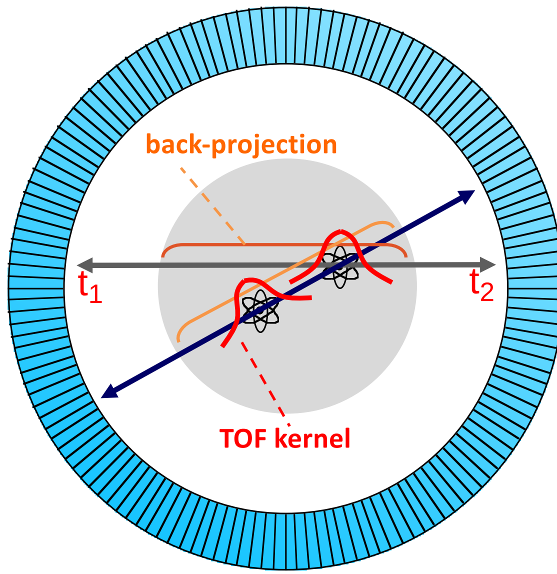
  Weber WA. Journal of Nuclear Medicine 2005; 46(6):983-995;
  Young H, et al. *Eur J Cancer* 1999; **35**(13):1773-1782.;
  Shankar LK, et al.. *Journal of Nuclear Medicine* 2006; **47**(6):1059-1066;
  Westerterp M, et al.. *European Journal of Nuclear Medicine and Molecular Imaging* 2007; **34**(3):392-404.
  Delbeke. *Journal of Nuclear Medicine* 2006; **47**(6):903

- Comprehensive review: R. Boellaard, "Standards for PET Imaging Acquisition and Quantitative Data Analysis" JNM 2009;50(5):11S-20S
  - Biologic factors (patient motion, uptake time, blood glucose level)
  - Technical errors (faulty dose calibrator cross calibration, not measuring residual left in syringe, infiltrated dose)
  - Physical factors (scan acquisition parameters, image reconstruction parameters, use of contrast agents, ROI used)

Lists approximate ranges and maximum effects for each, derived from published studies or unpublished data, to convey the magnitude of potential errors

Time-of-flight (TOF)

- If can precisely measure the difference in arrival time of the two coincident photons, can further restrict location of the annihilation.
- Allows the reconstruction to achieve higher SNR by approximately a factor of 2x.

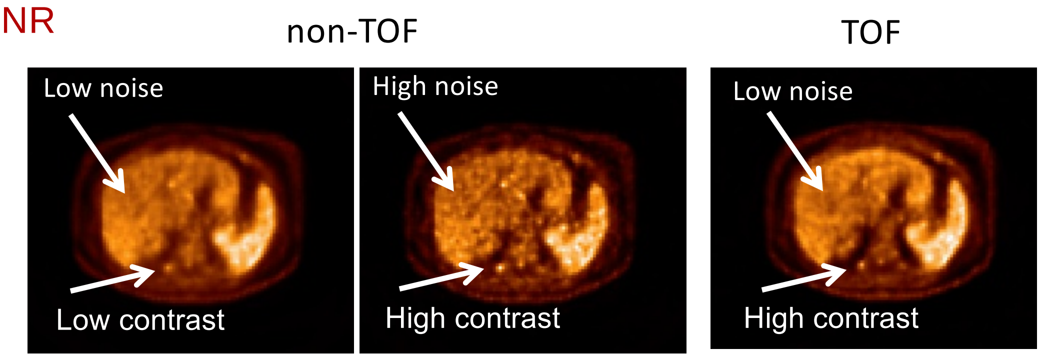


$\Delta t = t_1 - t_2$

$\Delta x = c \cdot \Delta t/2$

7.5 cm ~ 500 ps

TOF information reduces coupling of signals, thus improves SNR

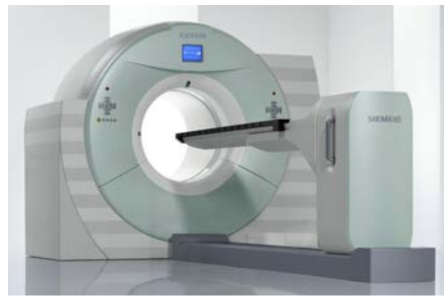


TOF PET/CT scanners from all vendors

PMT-based PET/CT: 2006 -> *Timing resolution 500-600 ps*

Philips Ingenuity TF

Siemens mCT



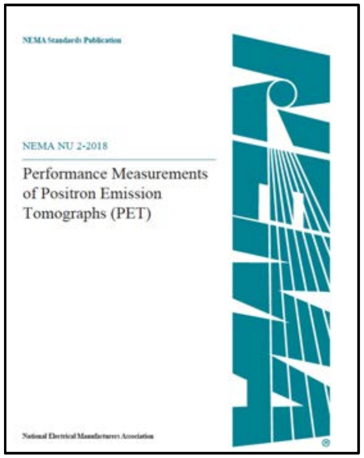
GE Discovery 690, 710

SiPM-based PET/CT: 2017 -> *Timing resolution 300-400 ps*

Philips Vereos

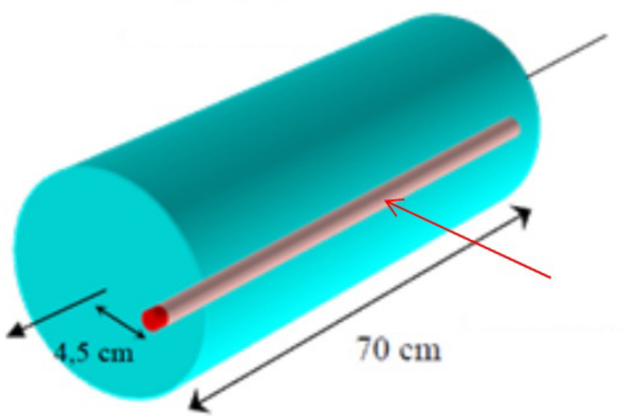
Siemens Vision

GE Discovery MI



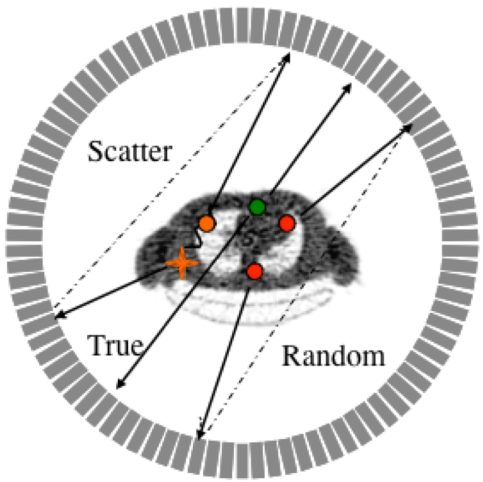
NEMA Measurements

- NEMA NU 2 Standard: instruction book on how to generate performance measurements that can be compared across manufacturers and models
- Must be revised periodically to include new capabilities, e.g. recent addition of Time of Flight Resolution measurement
- Currently includes recipes for sensitivity, spatial resolution, accuracy of corrections for count losses and randoms, accuracy of attenuation and scatter corrections, and:



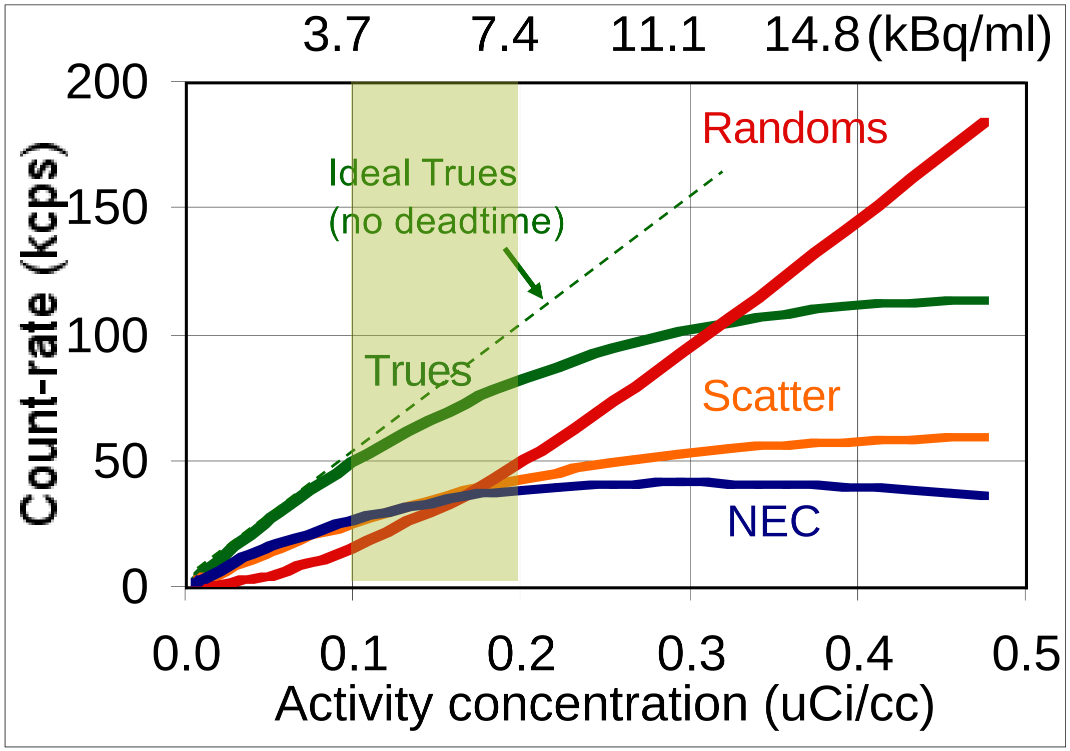
<u>Scatter Fraction, Count Losses, Randoms, TOF Resolution</u>

- 70 ± 2 cm line source of "relatively high activity" placed inside 70 cm long solid polyethylene cylinder
- Regular measurements taken while activity decays over several half-lives



Noise-equivalent count-rate

NEC = T/(1+S/T+R/T)



NEMA NU2-2001

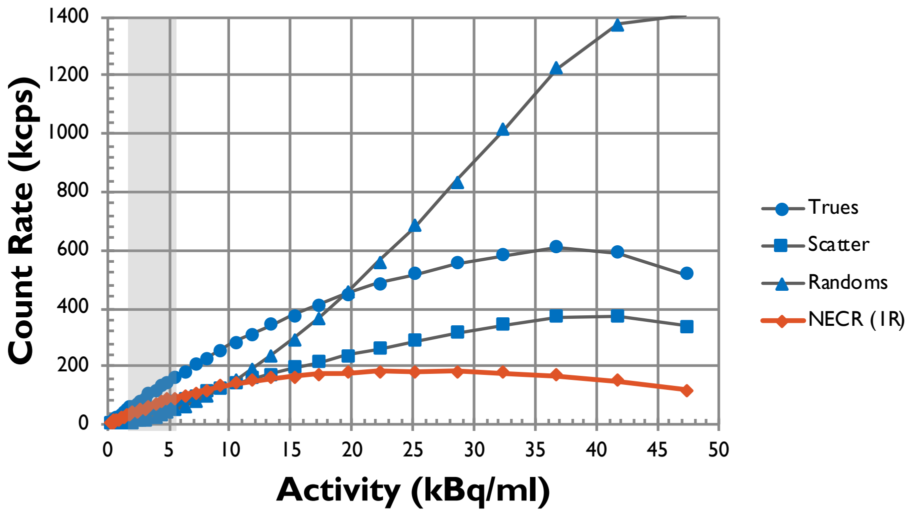
20-cm phantom

Philips *Allegro*
Univ. of Pennsylvania

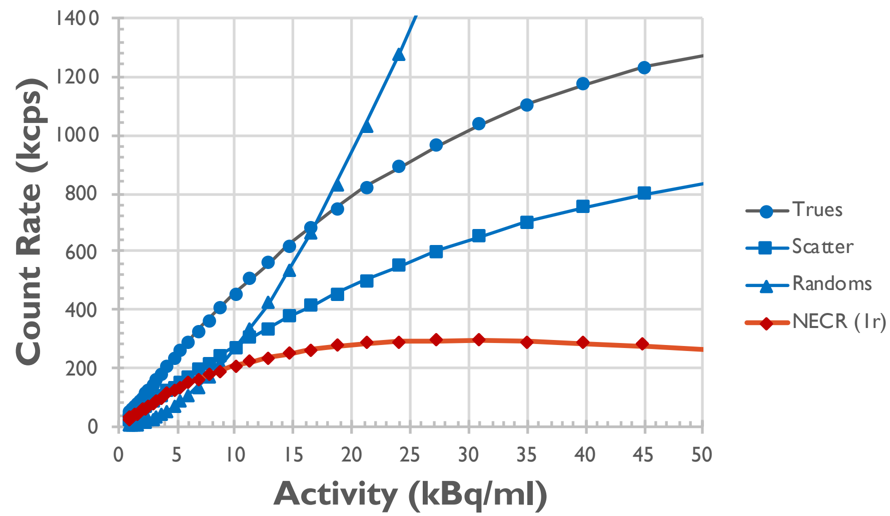
NECR comparison of two generations of PET/CT

NEC = T/(1+S/T+R/T)

Biograph mCT - 4 ring
PMT-based



Biograph Vision 600 Edge
SiPM-based



Peak NECR: 181 kcps at 25.2 kBq/ml

Peak NECR: 296 kcps at 30.9 kBq/ml

Comparison of two generations of scanner design

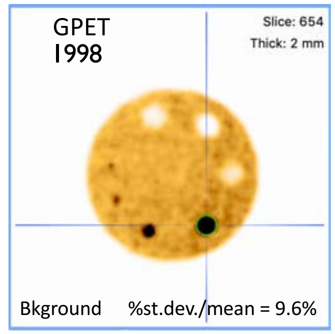
	Siemens Biograph Vision (2018)	Siemens Biograph 4-ring mCT (2011)
Energy Resolution	9.04%	11.3%
Spatial Resolution (axial)	3.6 mm at 1 cm; 4.3 mm at 10 cm	4.2 mm at 1 cm; 5.6 mm at 10 cm
Sensitivity	15.6 kcps/MBq at 10 cm	10.0 kcps/MBq at 10 cm
Peak Trues	> 1,323 kcps at 58.0 kBq/ml	609 kcps at 37.4 kBq/ml
Peak NECR	296 kcps at 30.9 kBq/ml	181 kcps at 25.2 kBq/ml
Scatter Fraction	39% at peak NECR	36% at peak NECR
TOF Resolution	215 ps FWHM at peak NECR	538 ps FWHM

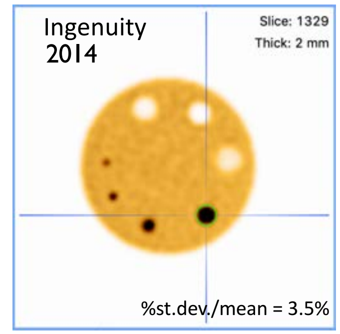
A multi-generational quantitative comparison

Smaller ACR PET phantom intended to simulate size of brain

Hot cylinders: 4 (not seen), 6, 8, 12, 16 mm
Cold cylinders: 16 mm water, teflon, air
Spheres (not inserted)

30 minute scans, 0.2 μCi/ml in background
2.6 contrast ratio, Hot: Background





		Target (mean):Background	Target (mean):Background
Hot	16 mm	2.18	1.99
	12 mm	1.93	1.84
	8 mm	1.59	1.60
	6 mm	1.44	1.53
Cold	water	0.23	0.24
	teflon	0.12	0.17
	air	0.51	0.35

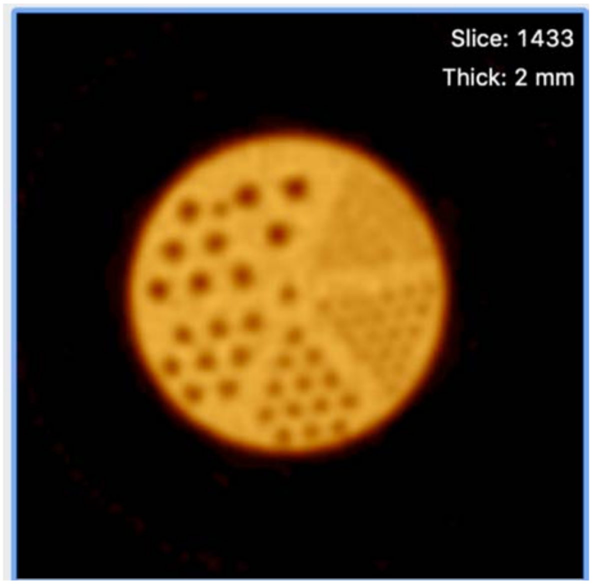
Ingenuity compared to GPET:

- ✓ 3x higher sensitivity due to improved crystal stopping power
- ✓ Improved uniformity due to more robust calibrations
- ✓ Similar quantitative accuracy, with improved performance for smaller structures due to TOF list mode OSEM reconstruction
- ✓ Faster, more accurate AC due to CT
- ✓ List data acquisition - limited only by disk space
- ✓ Choice of Brain (256 mm) and Body (576) FOV
- ✓ Service provider available

Image quality is better (i.e., more uniform) for Ingenuity but the quantitative accuracy is similar when comparing target:background of hot cylinders.

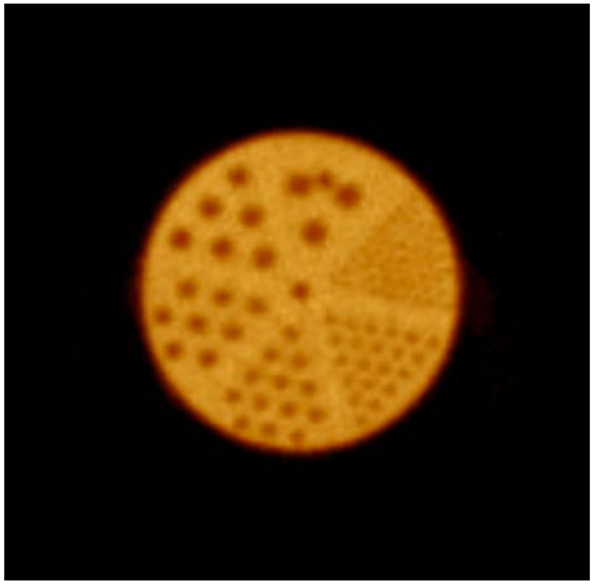
Spatial Resolution comparison

Ingenuity



Rod Sizes: 3.2, 4.8, 6.4, 7.9, 9.5, 11.1 mm

PennPET Explorer (2-rings only)



We will be performing phantom studies to optimize both image quality and quantitative accuracy for the PennPET Explorer, and to ensure consistency for studies that may transition from the Ingenuity.

The best way to ensure high quality, quantitatively accurate images is with a strong Quality Control (QC) program

- Series of tests performed regularly to ensure that the scanner is working as it should
- Program designed to identify problems BEFORE they impact the quality of patient studies
- Once a Quality Control/Quality Assurance program is in place, it must be reviewed periodically and updated as needed

Dose Calibrator QC

Daily

- Voltage Check
- Zero Adjustment
- Background Measurement
- Check Source Validation

Annual

- Accuracy
- Precision/Reproducibility
- Linearity

Daily QC for Philips Ingenuity PET/CT camera

Daily PET procedures

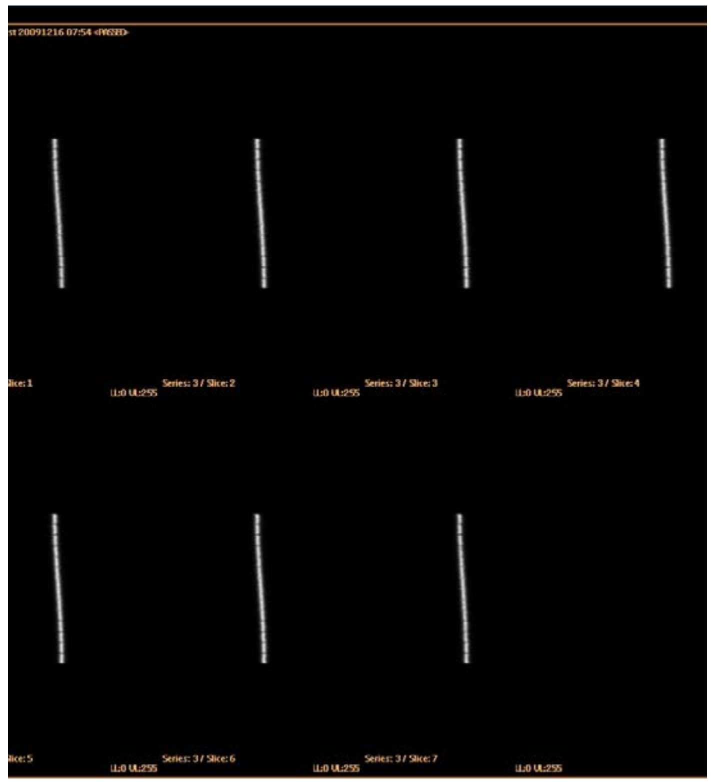
- Full system initialization
- Baseline collection (collection of analog offsets of all photomultiplier channels)
- Energy test and analysis
- PMT gain calibration
- Emission collection and sinogram analysis
- Test of timing resolution
- *PET/CT Test scan of Na-22 button source*

Daily CT procedures

- Tube conditioning
- Air Calibration
- Scan of mfg. CT QC phantom (water layer in head section, Teflon pin section in body section)

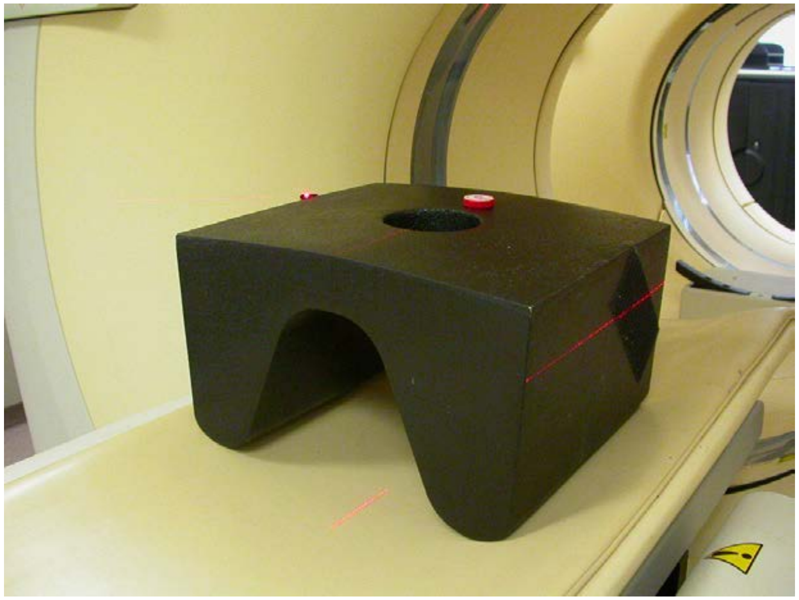
Emission Collection

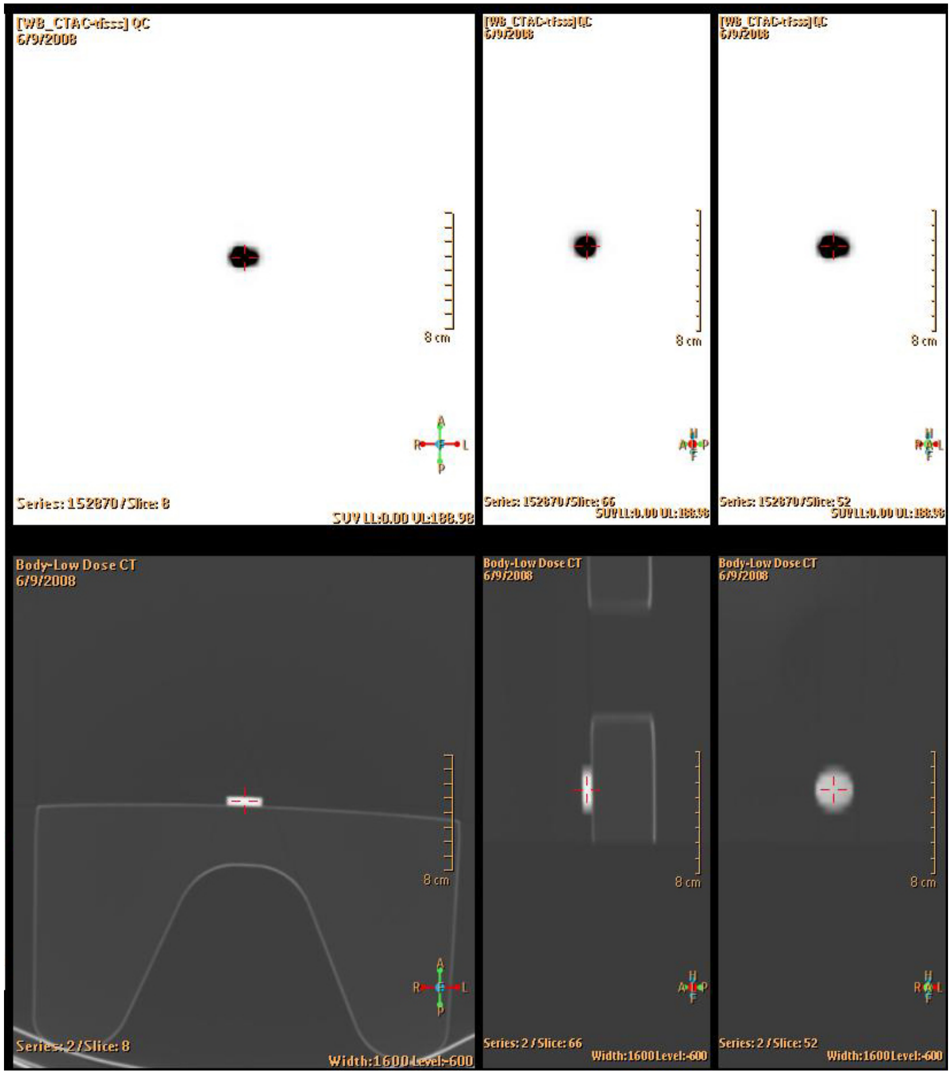
- Na-22 point source placed in the center of the FOV
- Emission collection is binned into sinograms
- Resulting image is checked for gaps in the "lines"



Additional daily QC – scan of Na-22 button source

- Check that PET and CT systems communicating with each other
- Check of alignment, table indexing (relative axial offset)

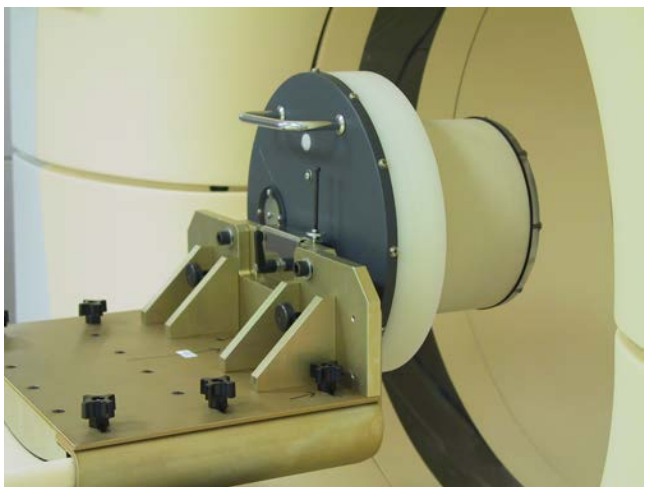


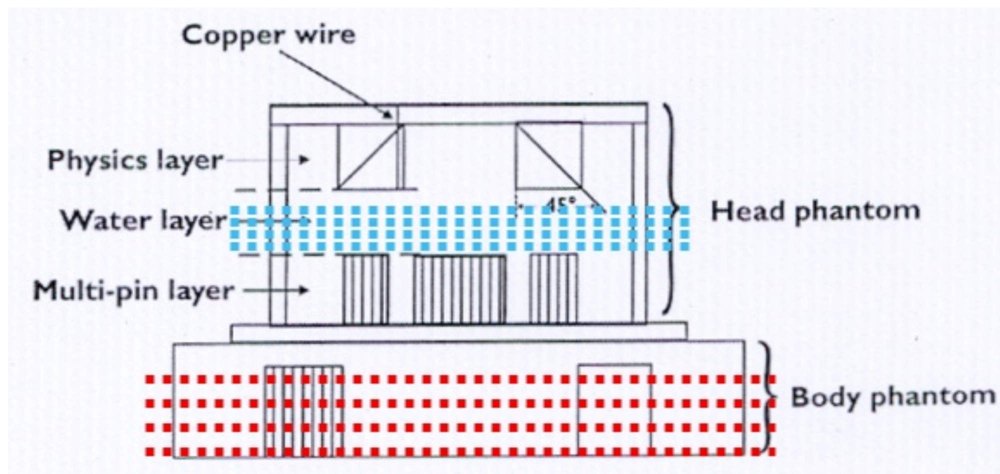


CT QC for Philips PET/CT camera

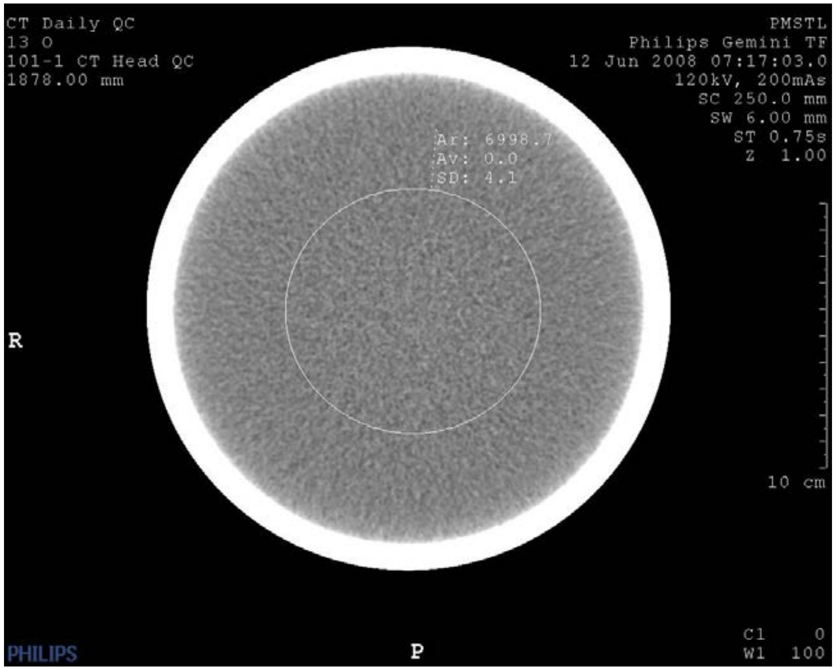
Daily procedures

- Tube Conditioning - warms the CT tube to operating temperature
- Scan of water layer of CT QC phantom's head section and of the Teflon pin section of that phantom's body section.
- Air Calibration – Scan of empty FOV to determine the HU of air, performed once or twice a week.





Analysis of Daily CT QC



Evaluate: a) image noise b) image uniformity, c) artifacts, d) average and sd of CT# for water, nylon, teflon pin.

Monthly QC for Philips PET/CT camera

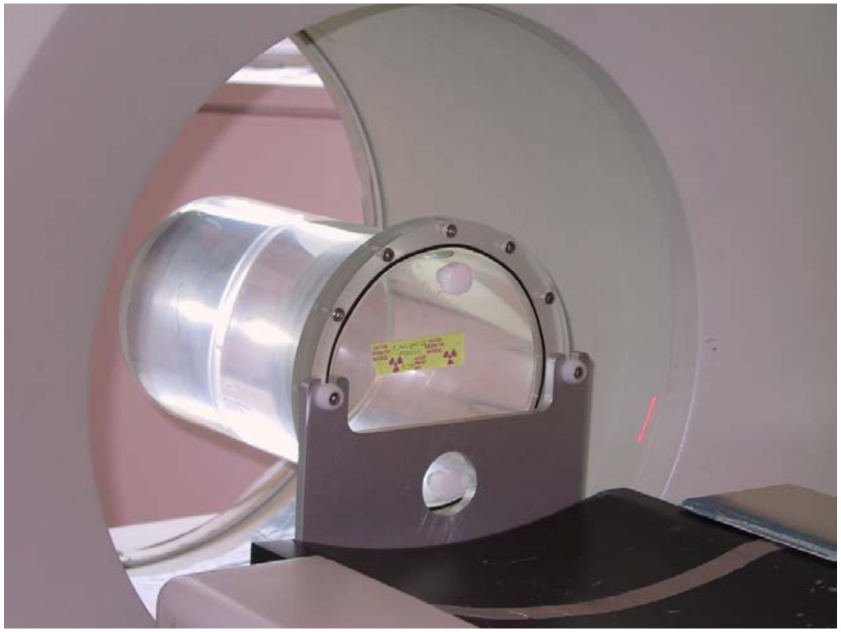
Monthly PET procedures

- Uniformity and SUV check by imaging a 20-cm diameter, 30-cm long uniform cylinder
- ACR Phantom (quarterly) checks contrast recovery and spatial resolution

Monthly CT checks

- CT Constancy
- Scan of multi-pin layer of CT QC phantom

Monthly Uniform Cylinder

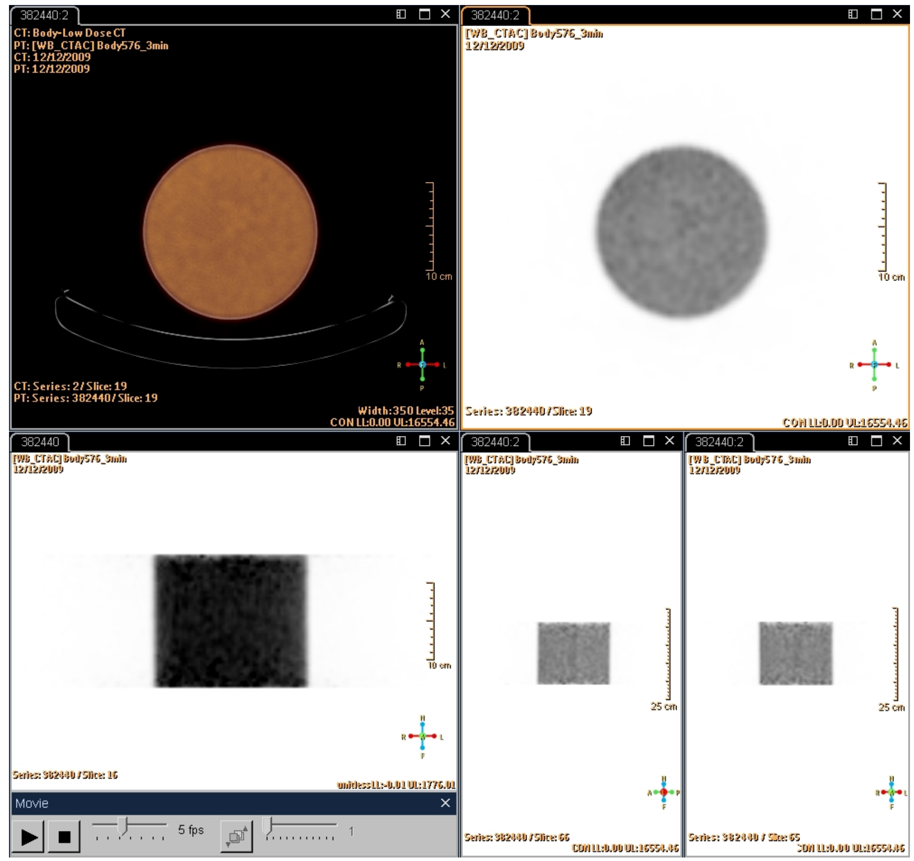


20 cm diameter x 30 cm long (Vol: 9,293 ml)

PET axial FOV: 18 to 26 cm so cylinder extends past FOV

Add: 1.5 to 2.0 mCi F-18

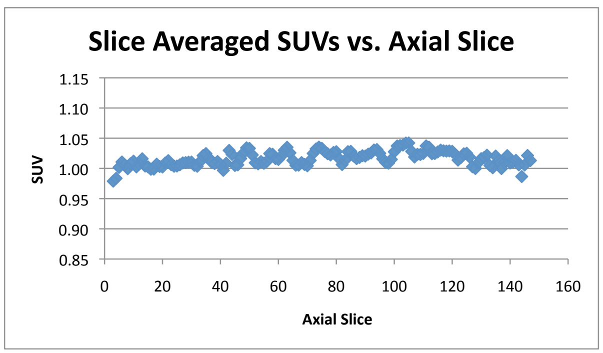
Scan and reconstruct with protocol used for patients

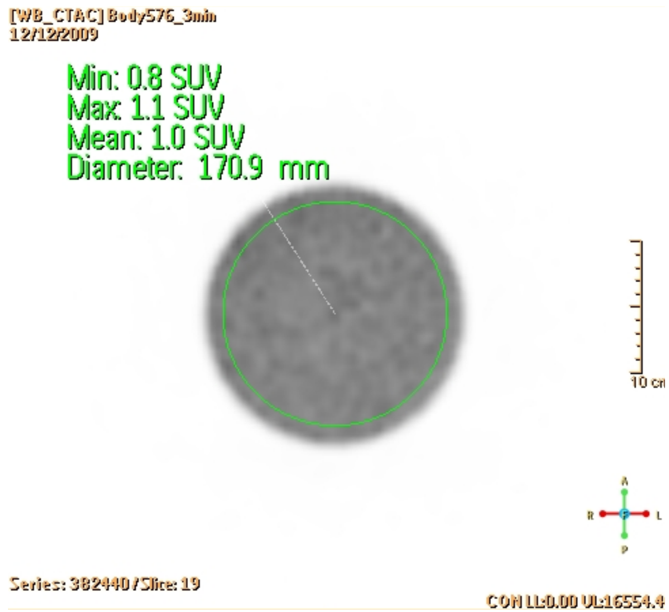


Quantitative Analysis of Uniform Cylinder

- Circular ROIs are drawn on each transverse slice
- Expected result is 1.00 ± 0.10

2D ROI Area:	228.70	cm^2
Volume Averaged SUV:	1.01	
Net Axial Variation:	5.56%	
Min Slice Averaged SUV:	0.98	on slice
Max Slice Averaged SUV:	1.04	on slice



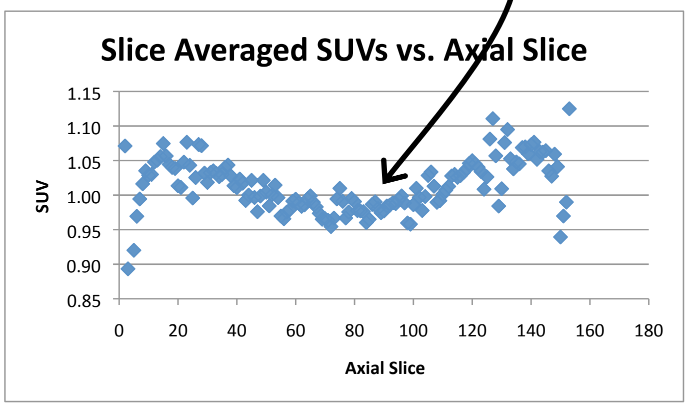


Also look at axial variation which should be < 10%.

Problematic results from other sites

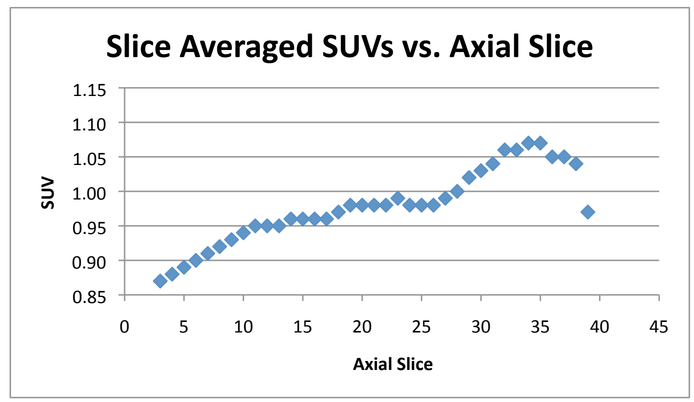
Dip in the center of the axial FOV could indicate a problem with the scatter correction

2D ROI Area:	216.33	cm^2
Volume Averaged SUV:	0.99	
Net Axial Variation:	108.58%	
Min Slice Averaged SUV:	0.00	on slice
Max Slice Averaged SUV:	1.08	on slice



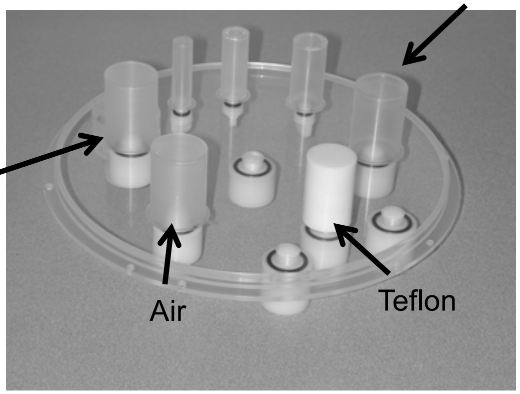
Systematic variation from one end of the axial FOV to the other can indicate a bad normalization or poorly mixed phantom

2D ROI Area:	217.21	cm^2
Volume Averaged SUV:	0.98	
Net Axial Variation:	20.44%	
Min Slice Averaged SUV:	0.87	
Max Slice Averaged SUV:	1.07	

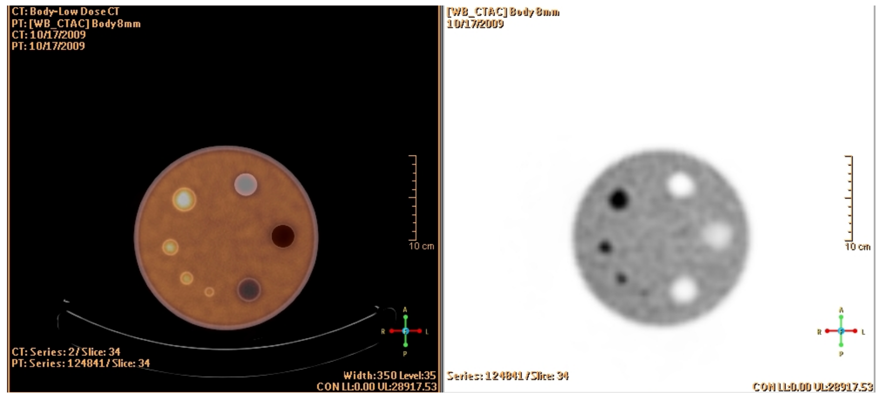


Quarterly ACR PET Phantom

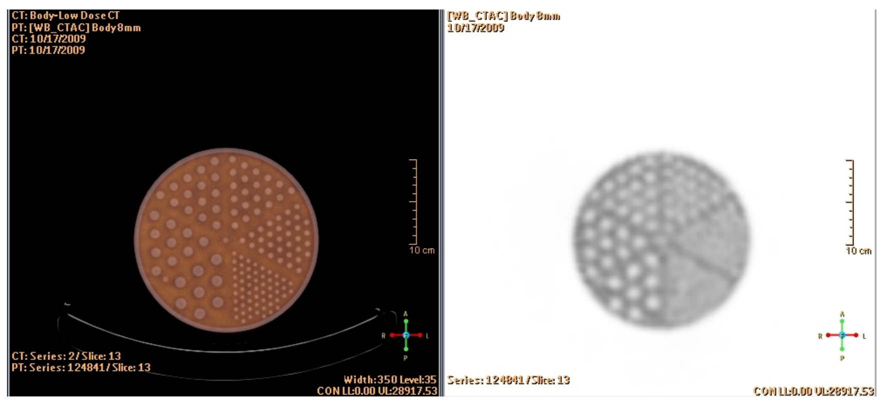
4 Hot Cylinders with diameters: 8, 12, 16, 25 mm



Flangeless Esser PET Phantom Lid™

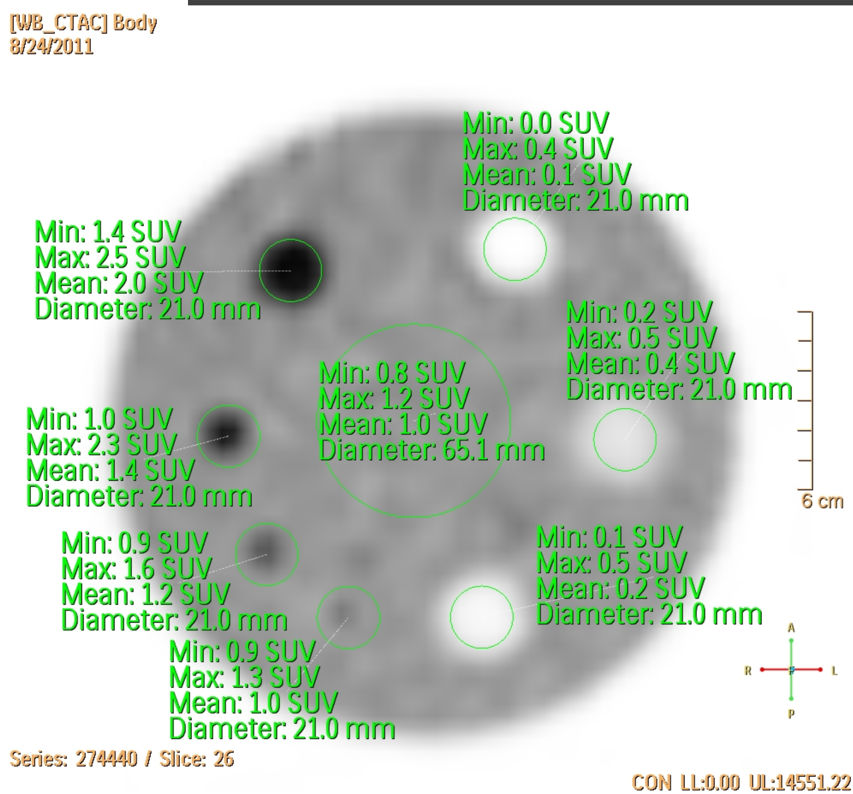


Flangeless Esser PET Phantom™



- Background activity concentration approximates 70 kg patient getting clinical injection
- Activity concentration is 2.5:1 between hot cylinders and background

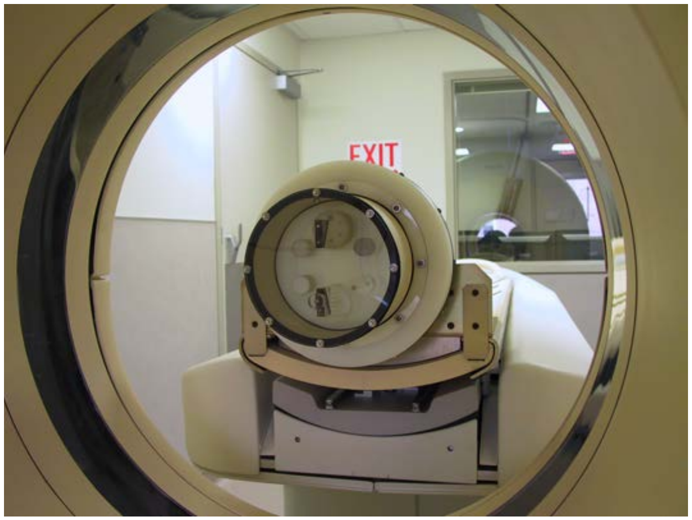
Analysis of ACR Phantom

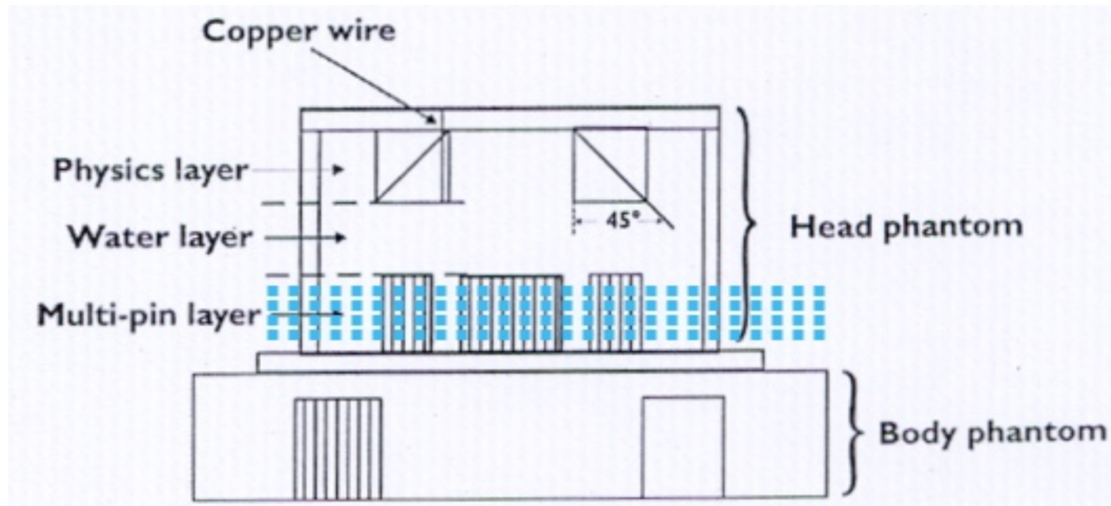


ACR Standards:

- Average Bkg. SUV:
  - 0.85 < SUV < 1.15
- 25mm Cyl. Max SUV:
  - 1.8 < SUV < 2.8
- Ratio 16mm/25mm Cyl:
  - Ratio > 0.7
- This phantom's results:
  - Bkg. Mean SUV = 1.0
  - 25mm Max SUV = 2.5
  - Ratio = 0.92

Monthly CT QC





Scan a different part of the CT QC phantom

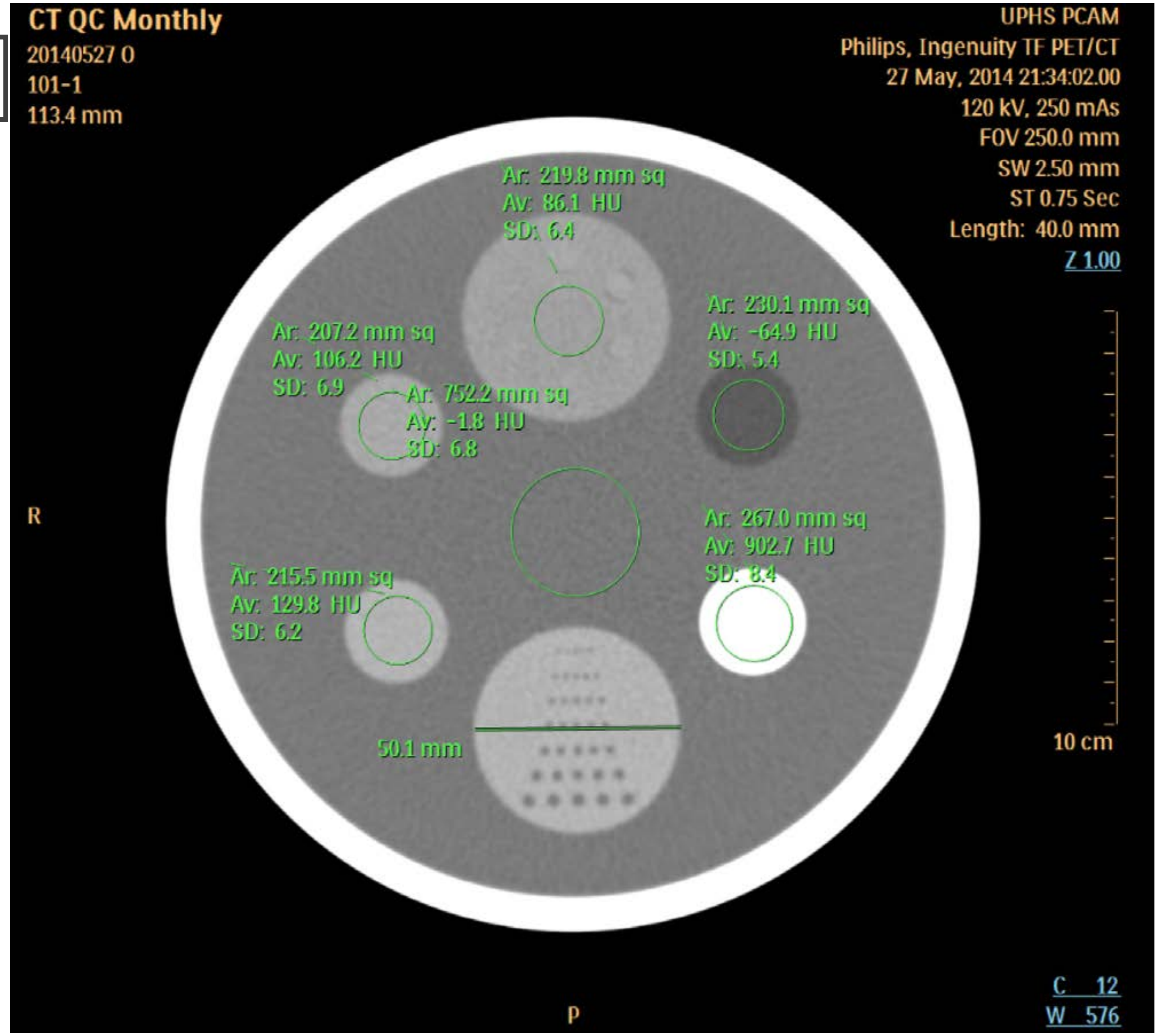
Analysis of Monthly CT QC

Evaluation of :

a) Measurement accuracy using diameter of large acrylic pin (50 ± 1 mm)
b) Resolution by checking that all 7 rows of resolution holes can be seen,
c) Contrast by checking that 5 of 6 low contrast pins can be seen,
d) Absorption (CT) numbers of 6 pins

- Expected Results

Region	Value
Water	0 ± 4
Nylon (Aculon)	+100 ± 15 (+10% relative to water)
Polyethylene	-75 ± 15 (-8% relative to water)
Teflon	+1016 ± 50 (+99% relative to water)
Acrylic	+140 ± 15 (+14% relative to water)
Lexan	+116 ± 15 (+12% relative to water)



Monthly CT Constancy

- Series of automated CT scans that measure phantom characteristics against baseline measurements
- Characteristics checked:
  - Homogeneity of Water Filled Region
  - Noise in a water-filled region
  - Slice Thickness
  - Modulation Transfer Function (MTF)
    - Surrogate for Spatial Resolution
  - Contrast

Annual QC

- Internal component checks (manufacturer)
- Recalibrations as needed
  - normalization, SUV, timing, distortion removal
- Annual physicist survey(s)

Content of Annual Physics Report

ACR Guidelines:

- Spatial Resolution
- Energy Resolution
- Timing Resolution
- Uniformity (Uniform Cylinder)
- ACR Phantom
- PET/CT Fusion
- Quality Assurance Program
- Video display
- Dose Calibrator QC

ACR-AAPM Technical Standard (2016): The following characteristics should be evaluated on at least an annual basis:

1. Spatial resolution
2. *Count rate performance (count rate versus activity), including count loss correction*
3. *Sensitivity (cps/MBq/mL)*
4. Image uniformity
5. Image quality
6. Accuracy of attenuation and scatter correction, and SUV measurement
7. Safety evaluation
   a) Mechanical b) Electrical

PET QC and CT QC but what about PET/CT QC?

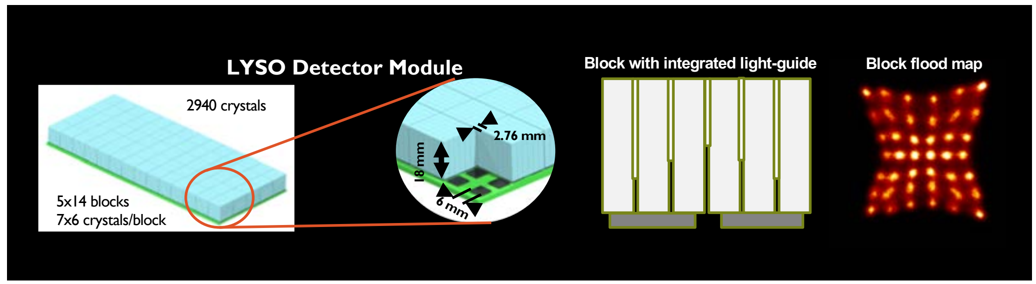
- Table travel must be extended and supported over longer distance
- Need agreement on absolute and relative coordinates between the two gantries
- Communication between the gantries

Long AFOV (Axial Field of View) scanners

uEXPLORER

194 cm AFOV

uEXPLORER PET Detectors: **10:1 encoding, crystals:SiPMs**



Courtesy, Hongdi Li, UIH America

- TOF = 509 ps, 3-mm spatial resolution

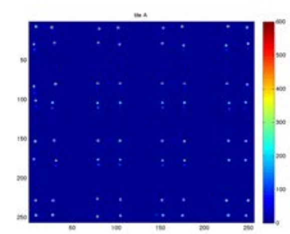
PennPET Explorer

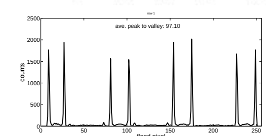
70 - 140 cm AFOV

PennPET Detectors: **1:1 encoding, crystals:SiPMs**

3.86 x 3.86 x 19 mm^3 LYSO
PDPC digital SiPM

2D flood





- TOF = 250 ps, 4-mm spatial resolution

Challenge of QC on Long Axial FOV cameras

Ben Spencer et al, MIC 2019

- For uniformity measurement line up 5 30-cm long uniform phantoms?
- For NEMA measurement of trues, scatter and randoms line up 3 70-cm long NEMA scatter phantoms?
- As we move towards having 6 rings of detector on the PennPET Explorer (=140 cm long AFOV), we will have to develop new QC procedures.

Acknowledgements

- Thanks to Joel Karp and Josh Scheuermann for contributing slides.