PHYSICS 428

LECTURE	DATE	INSTRUCTOR	TOPIC
1	April 2	PK	Overview: Imaging equation, inverse problem
2	April 9	PK	2D-LSI imaging systems, X-ray physics: formation and interaction
3	April 16	WH	X-ray detection and imaging systems
4	April 23	PK	X-ray computed tomography (CT) systems
5	April 30	WH	X-ray CT part 2. Contrast Agents
6	May 7	PK	Image reconstruction and image quality
7	May 14	LM	Nuclear decay schemes and isotopes
8	May 21	RM	Gamma cameras: components and systems
9	May 28	WH	Tomography in molecular imaging: SPECT scanners
10	June 4	SB	Positron emission tomography (PET) and hybrid PET/CT scanners
11	June 13	WH/PK	Group project presentations **

*** note change in date for class presentations to June 13th - Thursday instead of Tuesday*

Upcoming Friday June 7th deadline

- Group projects due to Prof. Kinahan
- Send at least one question on today's lecture with subject line "Phys 428 Lecture 10 Question" to Jackie (jackie24@uw.edu)

Positron emission tomography & hybrid PET/CT scanners

Stephen Bowen, Ph.D.

PHYSICS 428
June 4, 2013

srbowen@uw.edu

University of Washington
Medical Center
UW Medicine

Outline

I. Positron emission tomography

II. PET/CT scanners

III. PET/CT imaging uncertainties

IV. Advances & clinical applications

V. Q & A

Hallmarks of PET Imaging

- **PET is sensitive**
  - Efficient photon detection
  - PET sensitivity 10^3 greater than SPECT, 10^6 greater than MRI

- **PET is specific**
  - Many radiolabeled tracers of specific molecular pathways

- **PET is quantitative**
  - Accurate photon attenuation correction with CT
  - PET measures absolute activity concentration

- **PET has limitations**
  - Spatial resolution
    - clinical PET ~ 5 mm, small animal PET ~ 1 mm
  - Uncertainties
    - Image formation
    - Image analysis

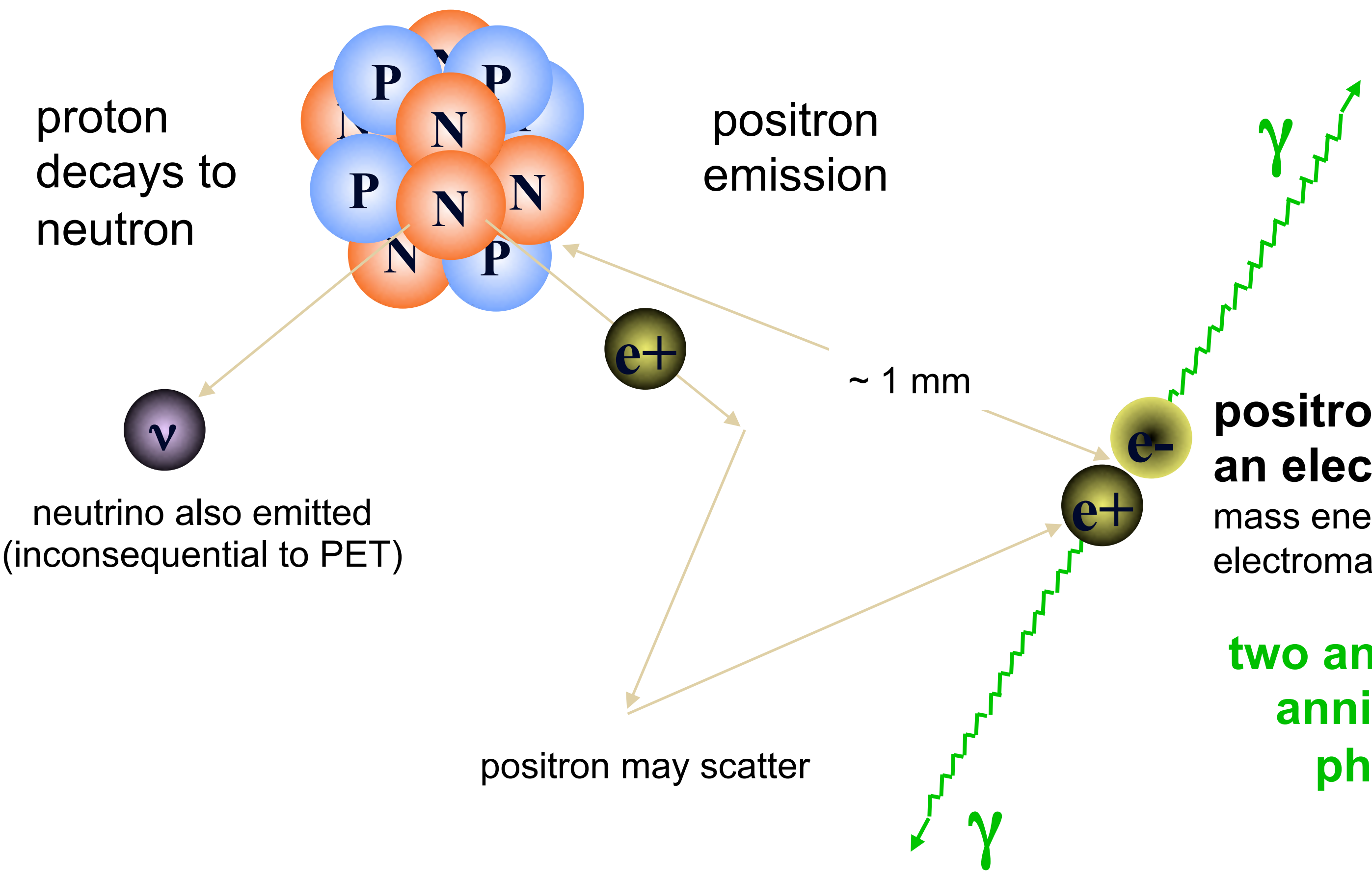
PET Definition

- **P**ositron
  - Uses **positron** (β^+) emitting radio-isotopes to label physiologic tracers
  - Positrons annihilate with electrons, resulting in two anti-parallel photons each with energy 511 keV
  - PET scanners measure coincident annihilation photons and localize the source of the decay
- **E**mission
  - The source of the signal is **emission** of annihilation photons from within the patient, as opposed to photons transmitted through the patient in x-ray imaging
- **T**omography
  - Slice-by-slice image reconstruction of 3D object through collection of projection data from all angles around the patient

Positron Annihilation

Parent nucleus:
unstable due to excessive P/N ratio

$^{18}F \longrightarrow {}^{18}O + \beta^{+} + \nu$



positron annihilates with an electron:
mass energy is converted to electromagnetic energy resulting in

two anti-parallel annihilation photons

Positron Decay Questions

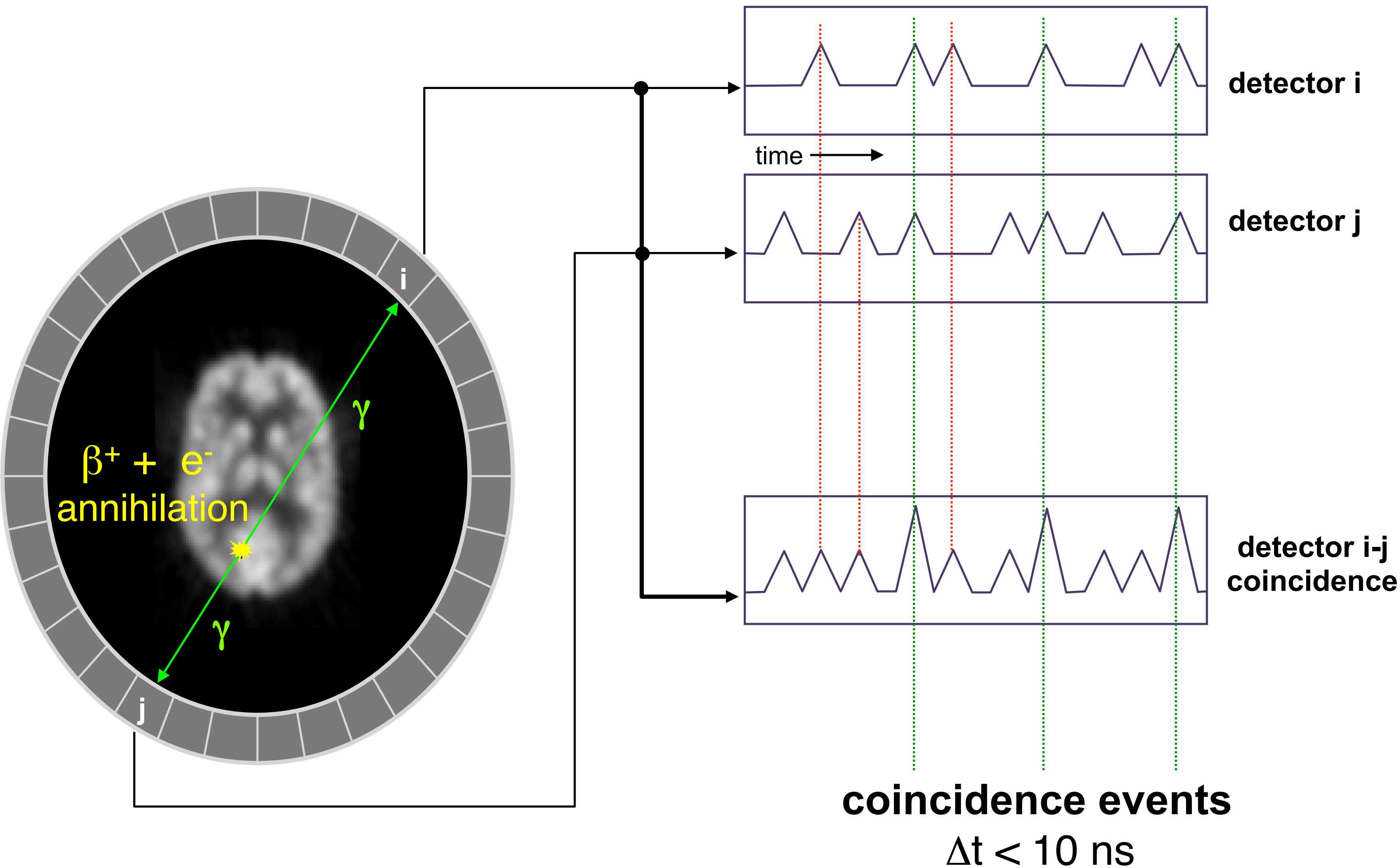
1. ${}^{13}_{7}N$ decays to which daughter nucleus?

   A ${}^{15}_{8}O$ B ${}^{13}_{6}C$ C ${}^{12}_{7}N$ D ${}^{14}_{9}F$ E ${}^{11}_{5}B$

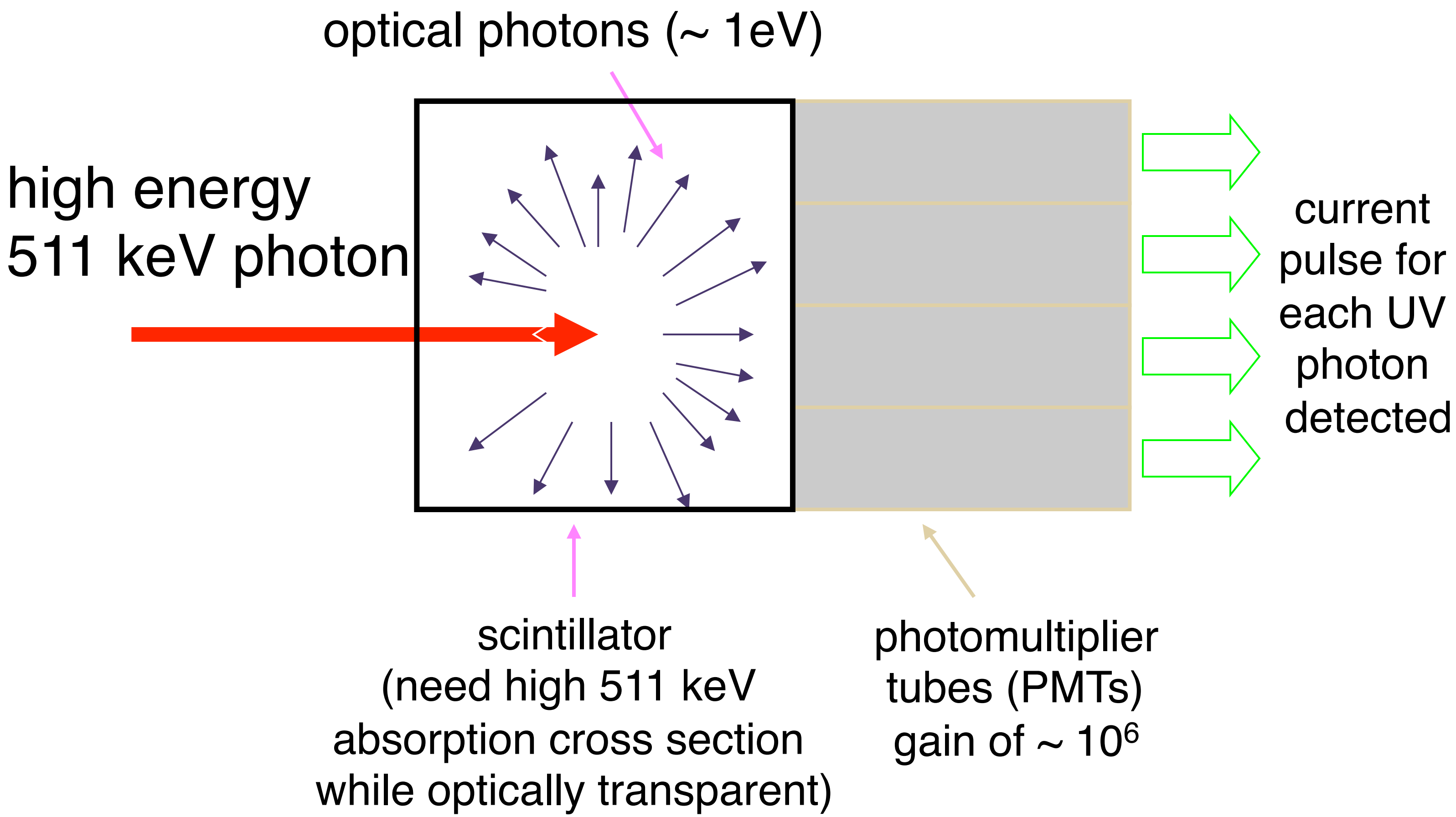
2. Which is NOT a positron emitter used in PET?

   A ${}^{9}_{5}B$ B ${}^{11}_{6}C$ C ${}^{13}_{7}N$ D ${}^{15}_{8}O$ E ${}^{18}_{9}F$

Emission Coincidence Detection

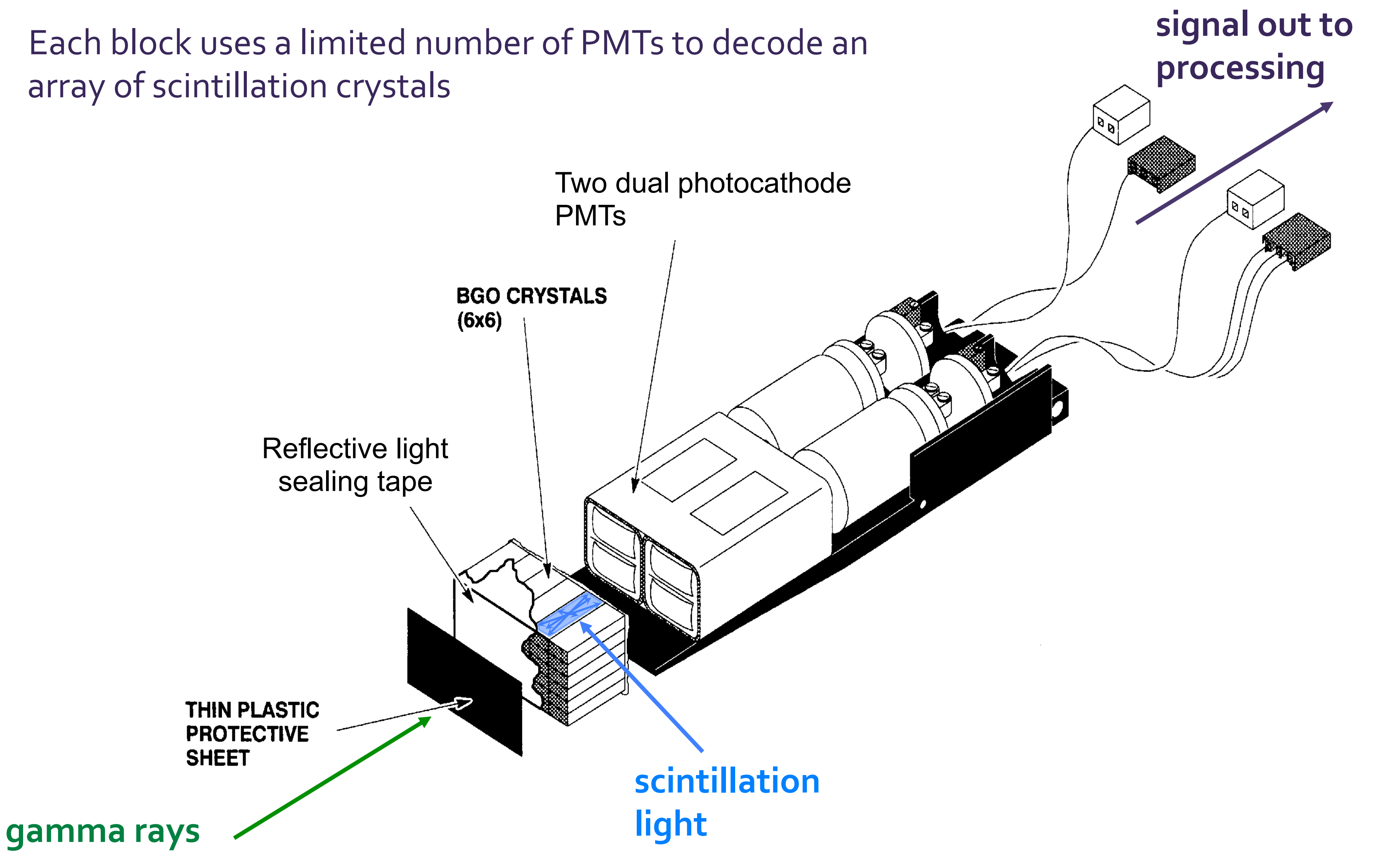


Scintillation

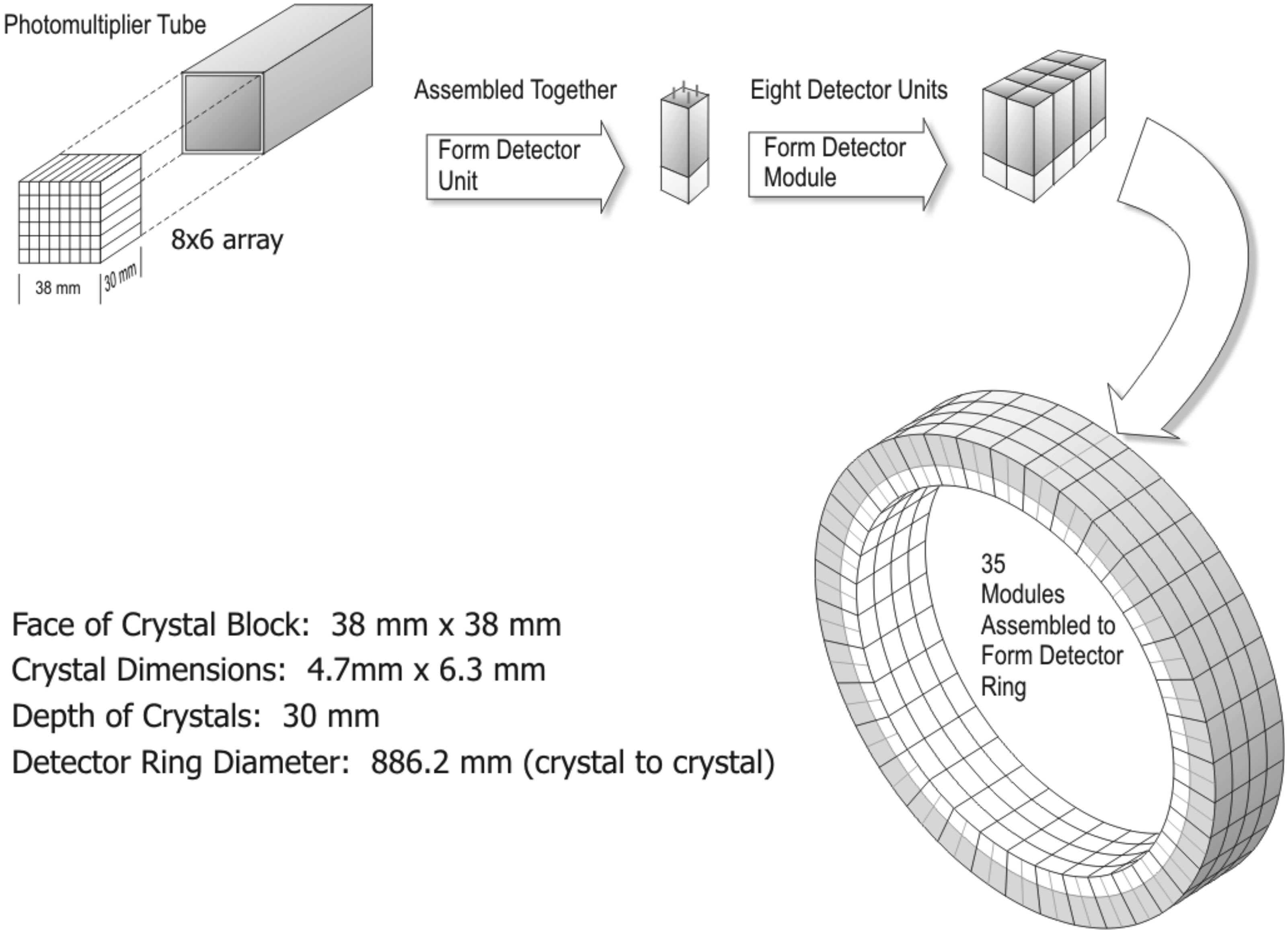


PET Detector Block

- PET scanners are assembled in block modules
- Each block uses a limited number of PMTs to decode an array of scintillation crystals



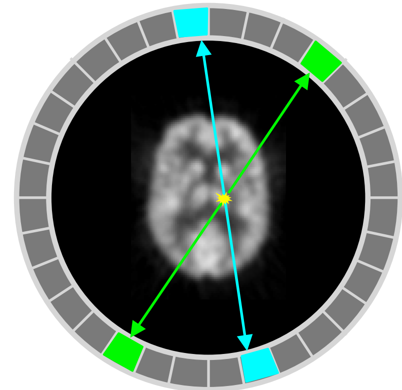
PET Scanner Detector Ring



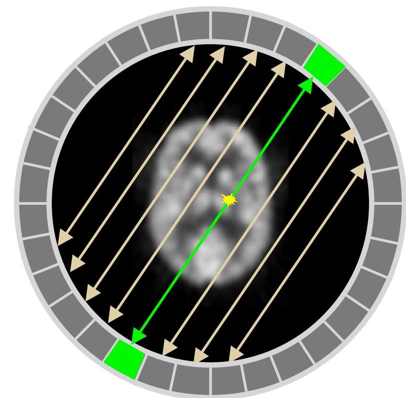
Face of Crystal Block: 38 mm x 38 mm
Crystal Dimensions: 4.7mm x 6.3 mm
Depth of Crystals: 30 mm
Detector Ring Diameter: 886.2 mm (crystal to crystal)

Tomographic Data Acquisition

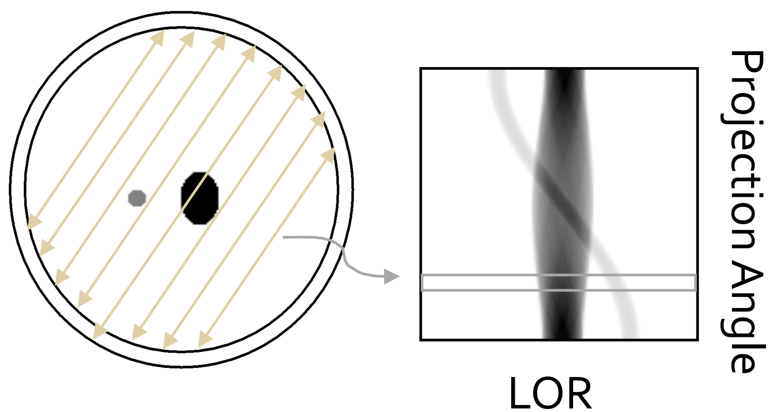
All coincidence events acquired over time allows dynamic imaging



Group coincidence data into parallel projections (LOR) for tomographic reconstruction

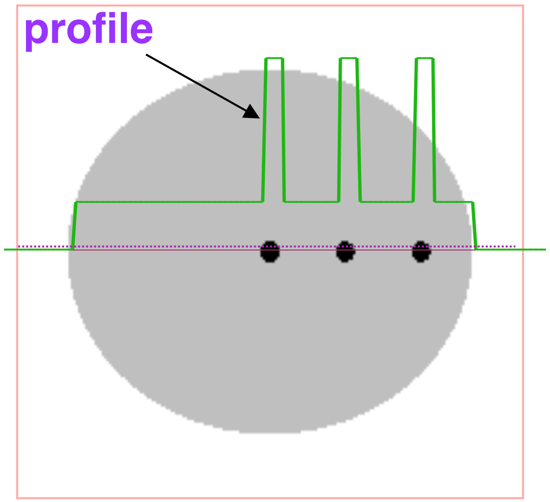


Sort LOR into <u>sinograms</u> and/or save <u>list-mode</u> data

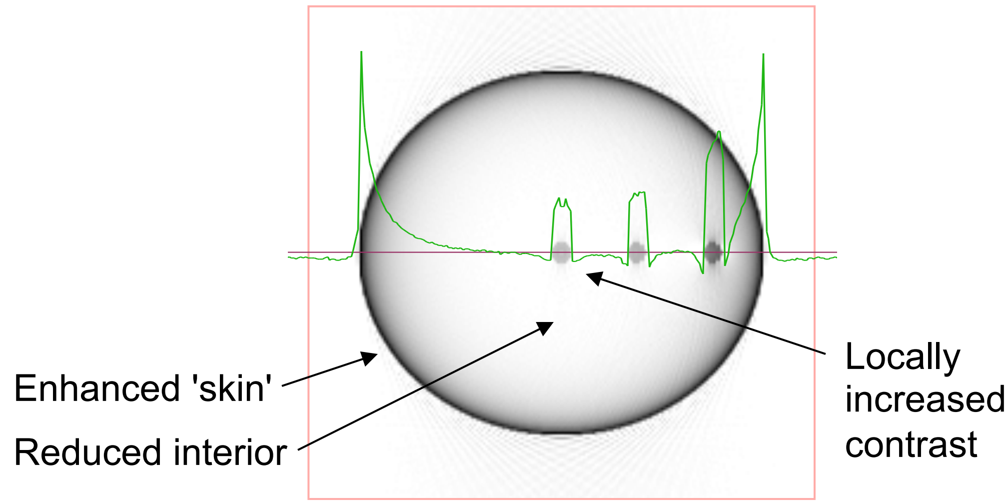


Annihilation Photon Attenuation

- Mathematics to describe the behavior without attenuation correction are complex
- Best thing is to have accurate attenuation correction



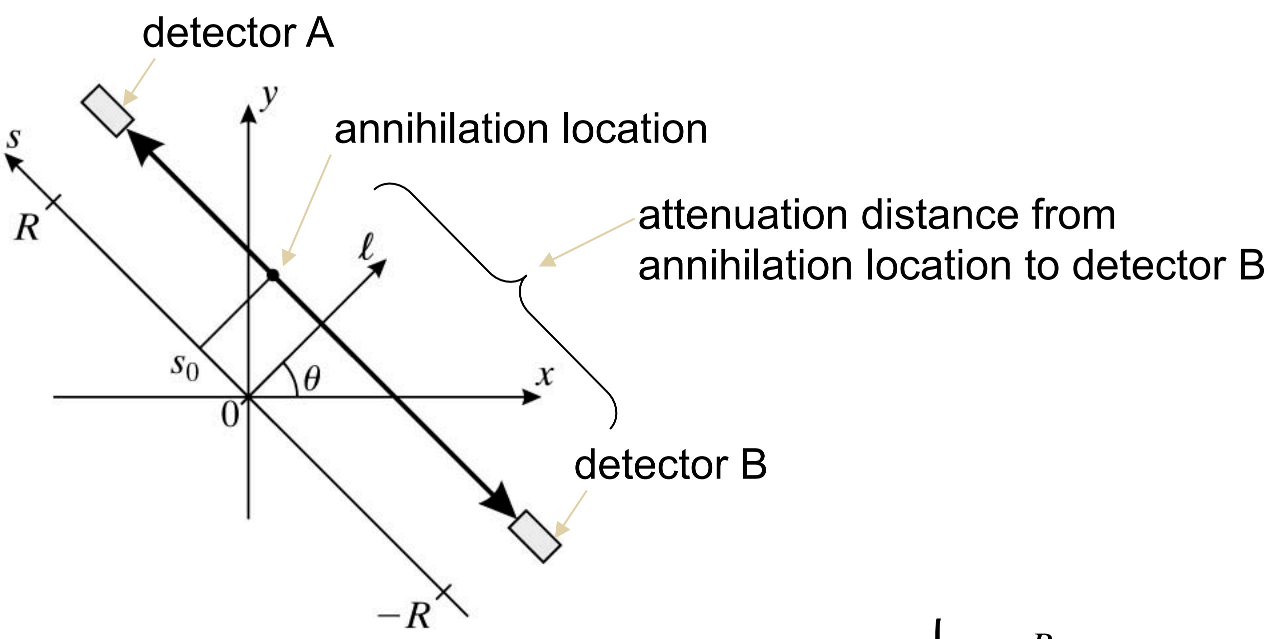
True PET image
(simulation of abdomen)



PET image without attenuation correction

Attenuation in PET Imaging

- 2 photons along the line of response (LOR)



photons detected from a single annihilation location at s_0

$$\begin{cases} N_A = N_0 \exp\left\{ -\int_{s_0}^{R} \mu(x(s'), y(s'); E)\, ds' \right\} \\ N_B = N_0 \exp\left\{ -\int_{-R}^{s_0} \mu(x(s'), y(s'); E)\, ds' \right\} \end{cases}$$

Attenuation in PET Imaging

- Total number of annihilation photons arriving in coincidence is the product of the attenuation factors

$$N_C = N_0 \exp\left\{-\int_{S_0}^{R} \mu(x(s'),y(s');E)\,ds'\right\} \exp\left\{-\int_{-R}^{S_0} \mu(x(s'),y(s');E)\,ds'\right\}$$
$$= N_0 \exp\left\{-\int_{-R}^{R} \mu(x(s'),y(s');E)\,ds'\right\}$$

- If we now allow for a distributed source of positrons

$$\phi(l,\theta) = K\int_{-R}^{R} A(x(s),y(s)) \exp\left\{-\int_{-R}^{R} \mu(x(s'),y(s');E)\,ds'\right\} ds$$

even better we have attenuation as a simple multiplication

$$\phi(l,\theta) = K\int_{-R}^{R} A(x(s),y(s))\,ds \cdot \exp\left\{-\int_{-R}^{R} \mu(x(s),y(s);E)\,ds\right\}$$

PET Imaging Equation

- Since attenuation can be factored out, and thus corrected by an independent measure, we have a simple 2D x-ray (Radon) transform of line integrals that can be exactly solved by filtered backprojection

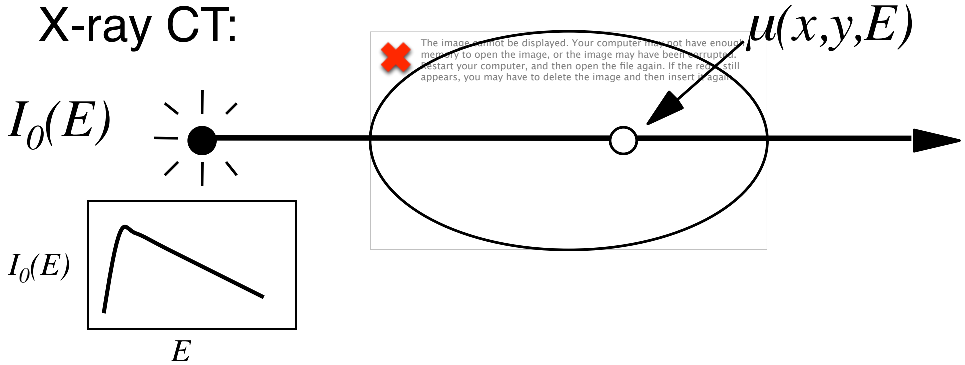
Imaging equation $\phi(l,\theta) = K\int_{-R}^{R} A(x(s),y(s))ds$

FBP solution $A(x,y) = \int_0^{\pi}\left[\int_{-\infty}^{\infty}|\rho|\Phi(\rho,\theta)e^{j2\pi\rho l}\,d\rho\right]d\theta$

where $\Phi(\rho,\theta) = \mathrm{F}_{\mathrm{1D}}\{\phi(l,\theta)\}$

Comparing X-ray, γ-camera (SPECT) and PET

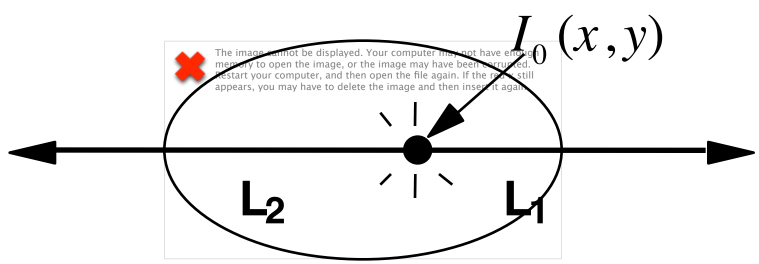
X-ray CT:



$$I = \int_0^\infty \left(I_0(E)\, e^{-\int_0^L \mu(x,y,E)\,dL} \right) dE$$

Attenuation only, but with <u>complicated</u> energy weighting

PET:

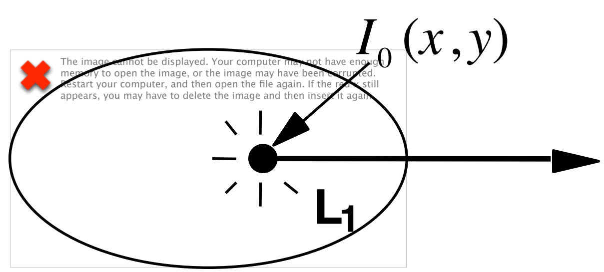


constant attenuation length: $L_1 + L_2 = L$

$$I = \overbrace{\left(\int_{-\infty}^{\infty} I_0(x,y)\, dL \right)}^{\text{emission (sinogram) data}} \cdot \overbrace{\left(e^{-\int_{-\infty}^{\infty} \mu(x,y,511keV)\, dL} \right)}^{\text{attenuation factors}}$$

Uncoupled mono-energetic attenuation and emission

SPECT:

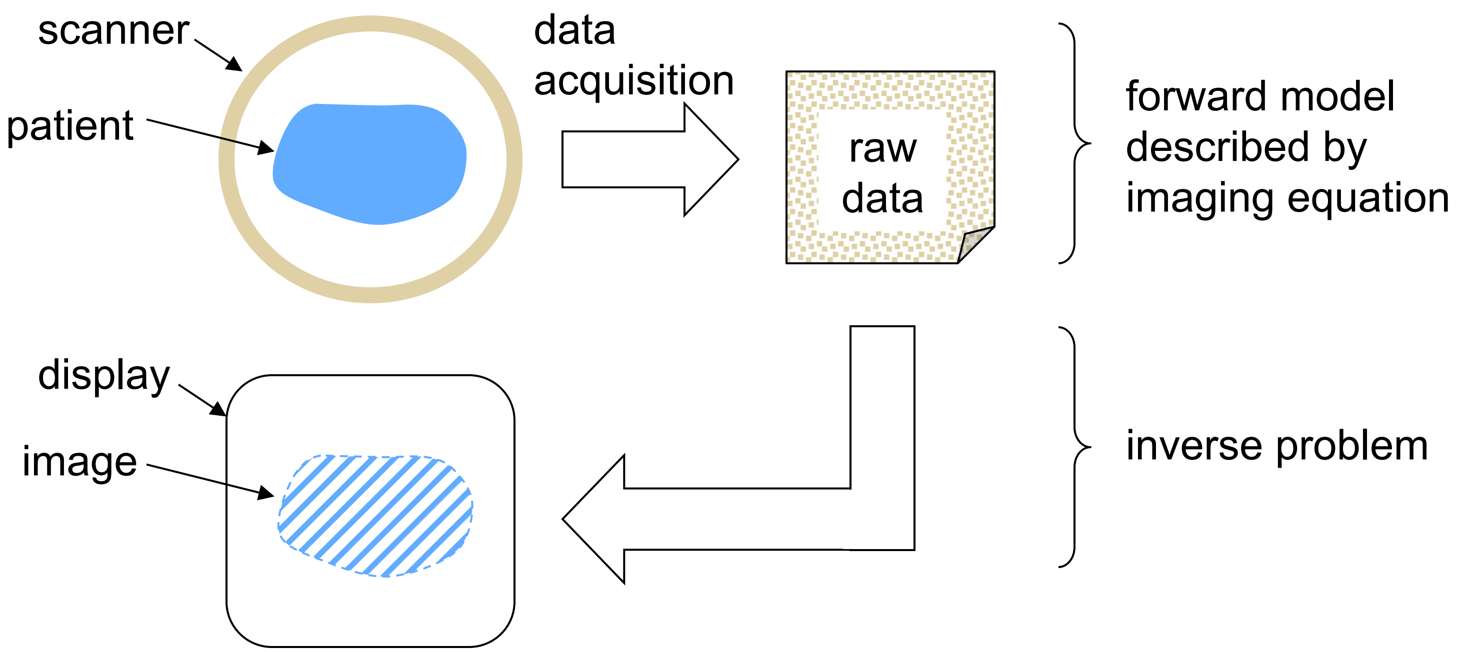


variable attenuation length: L_1

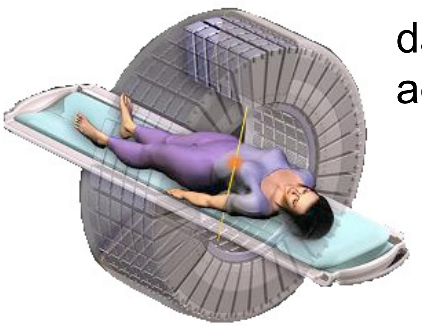
$$I = \int_0^L I_0(x,y)\, e^{-\int_0^L \mu(x,y,E_O)\,dL}\, dL$$

Coupled mono-energetic attenuation and emission <u>(complicated)</u>

Biomedical Imaging Systems: Concepts



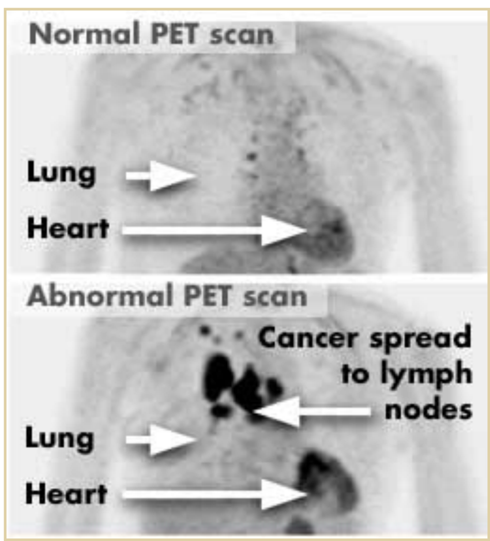
Biomedical Imaging Systems: Outline



data acquisition

raw data

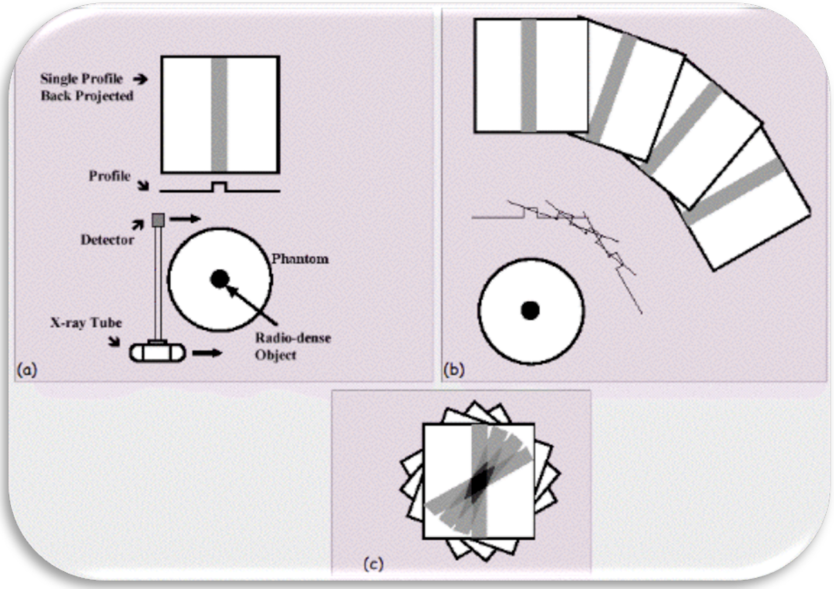
forward model described by imaging equation



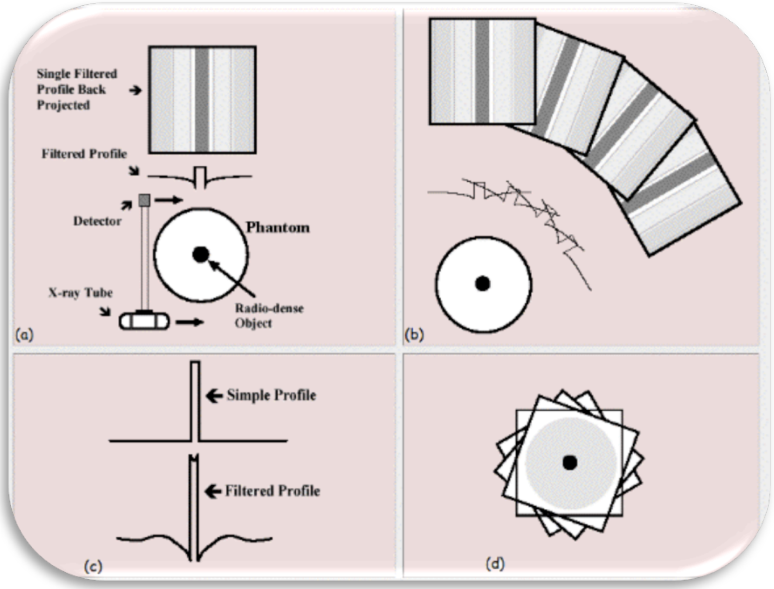
inverse problem

Analytic Reconstruction

Backprojection



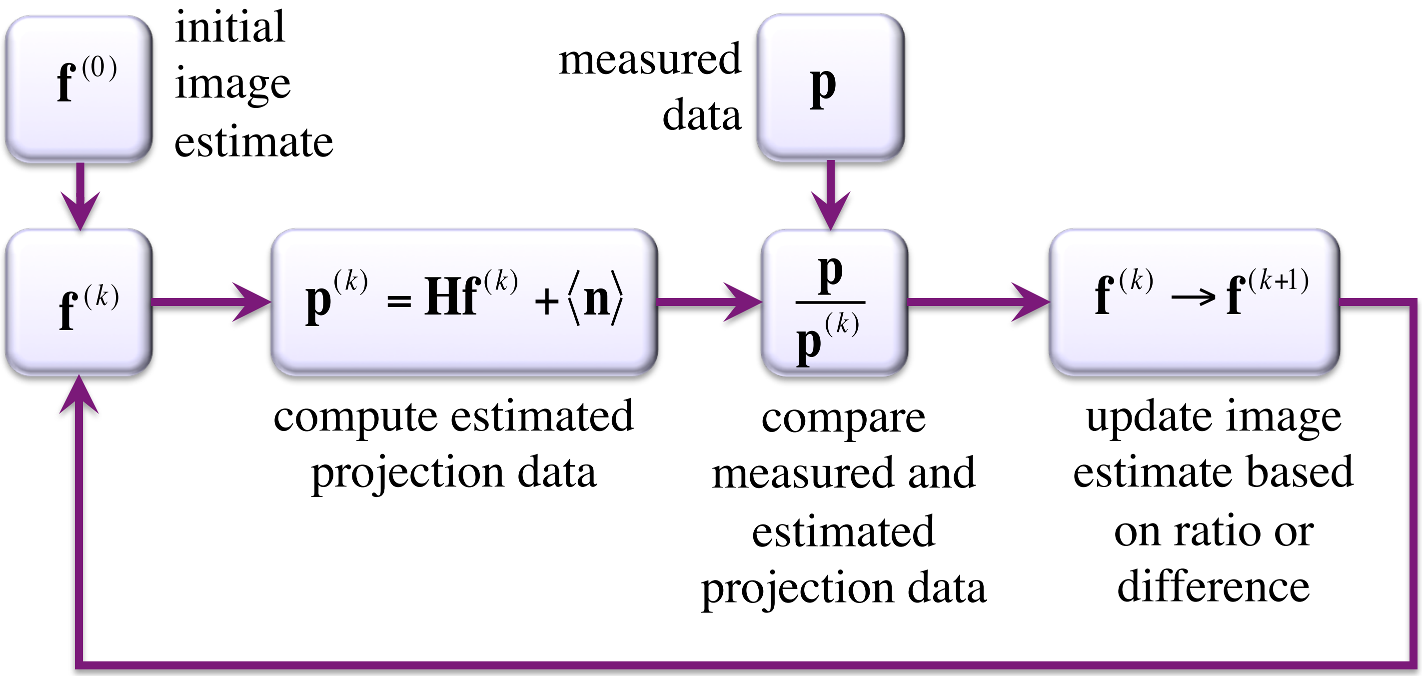
Filtered Backprojection



From WikiBooks *Basic Physics of Digital Radiography*

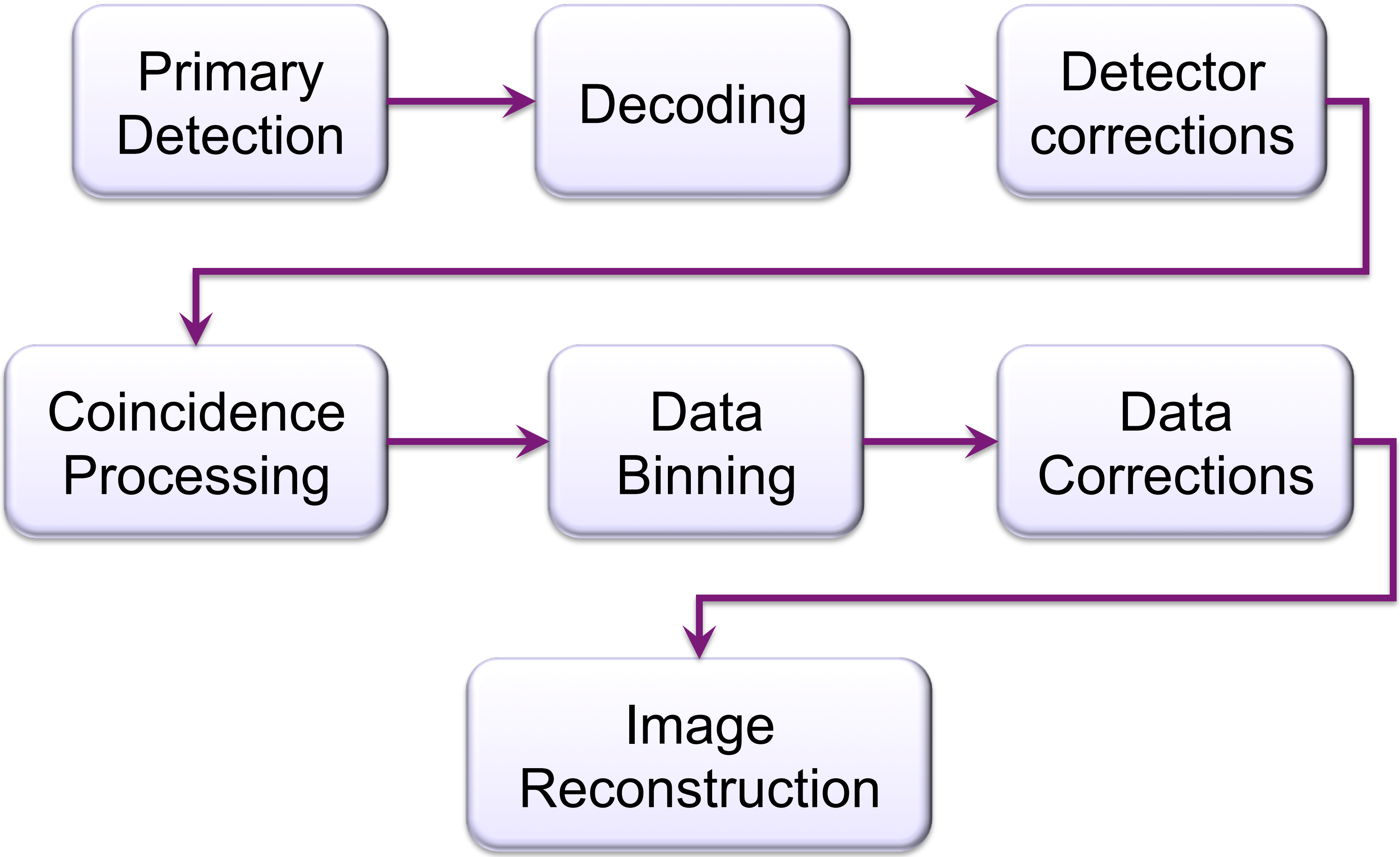
- FBP assumes linear projections and does not account for many sources of variability in LOR
- Backprojection leads to streak artifacts in PET images

Iterative Reconstruction

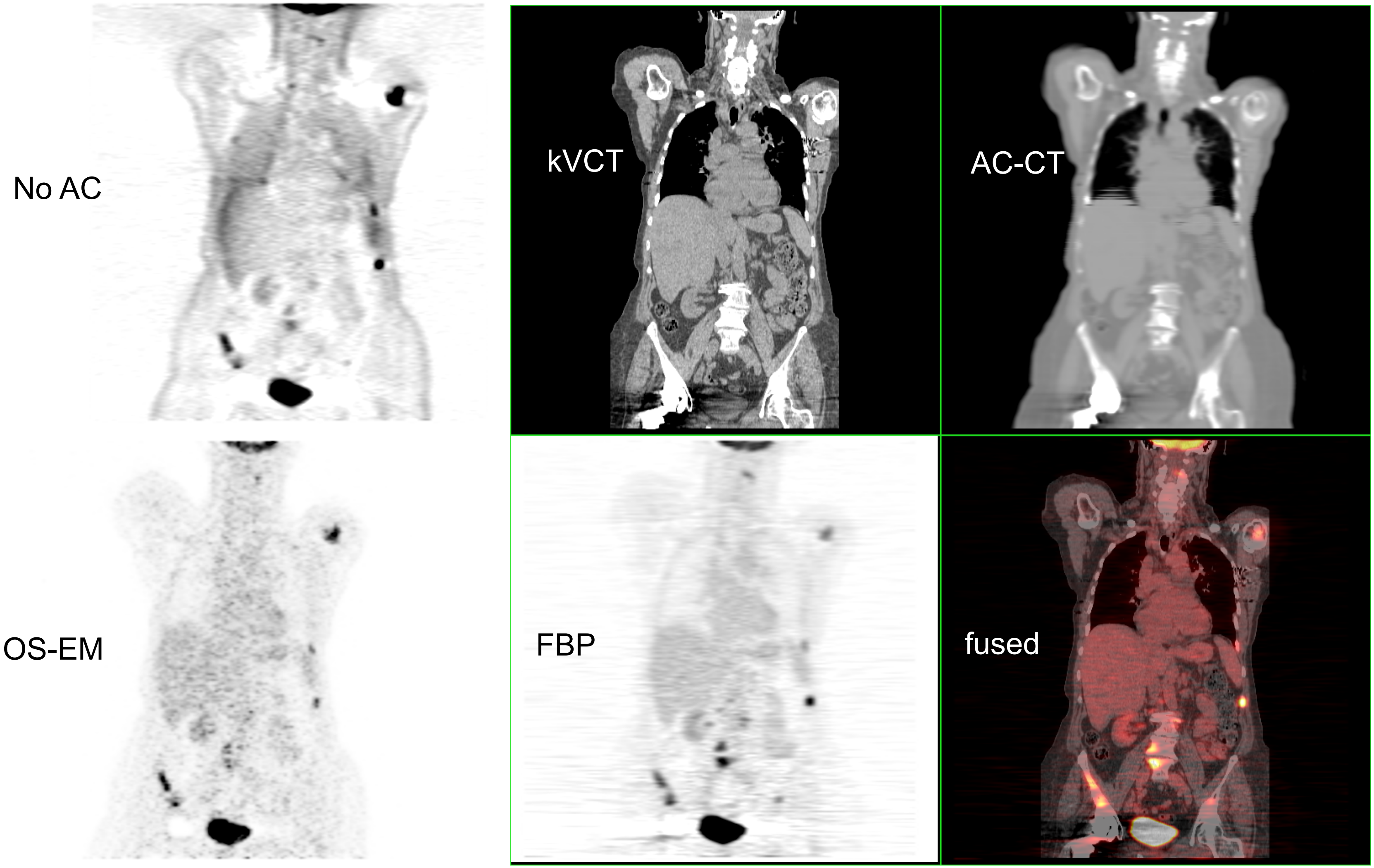


- There are many ways to:
  - model the system (and the noise)
  - compare measured and estimated projection data
  - update the image estimate based on the differences between measured and estimated projection data
  - decide when to stop iterating

PET Image Formation Workflow



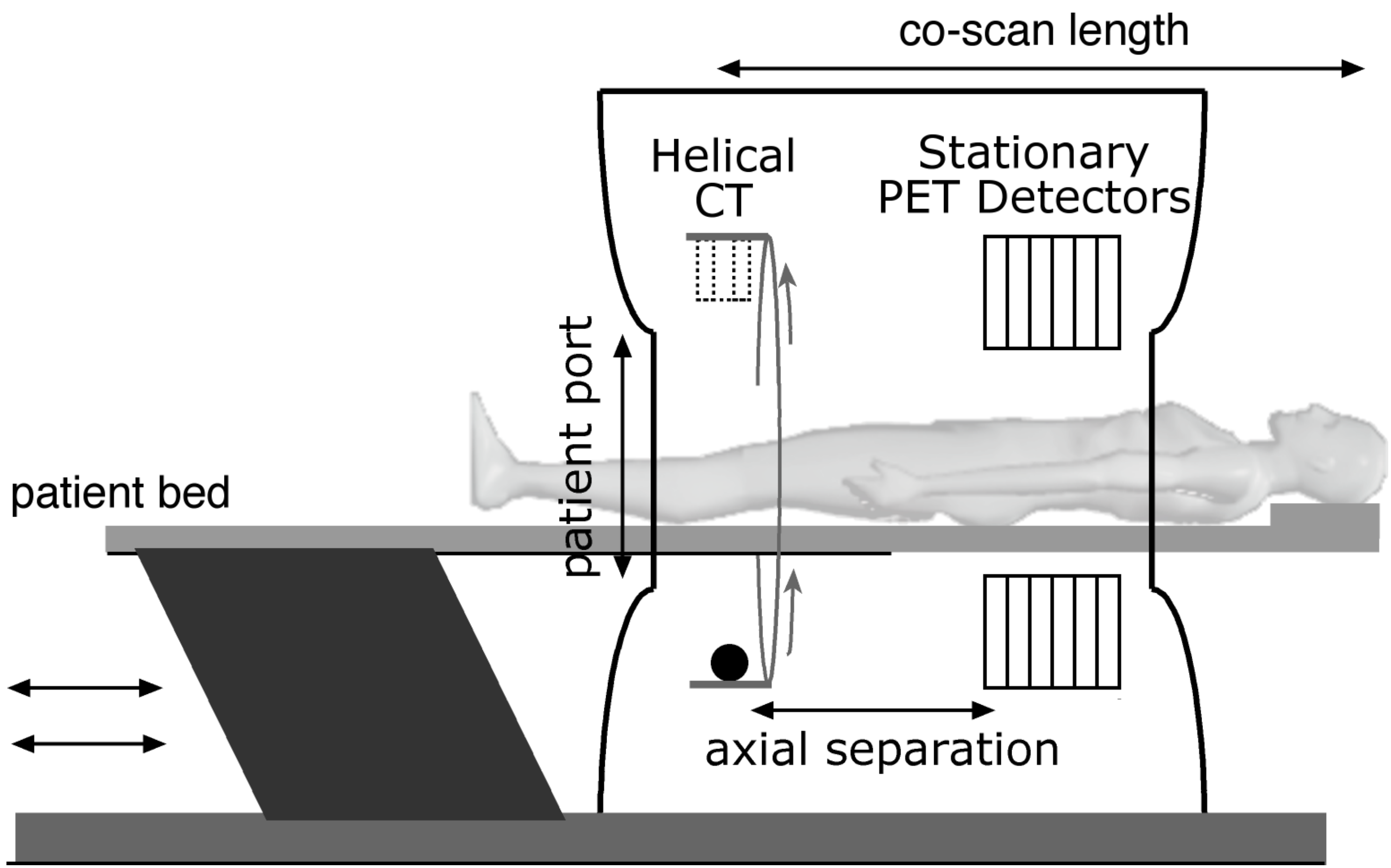
Reconstructed PET/CT images



AC: Attenuation Correction
OS-EM: Ordered Subsets Expectation Maximization
FBP: Filtered Back-Projection

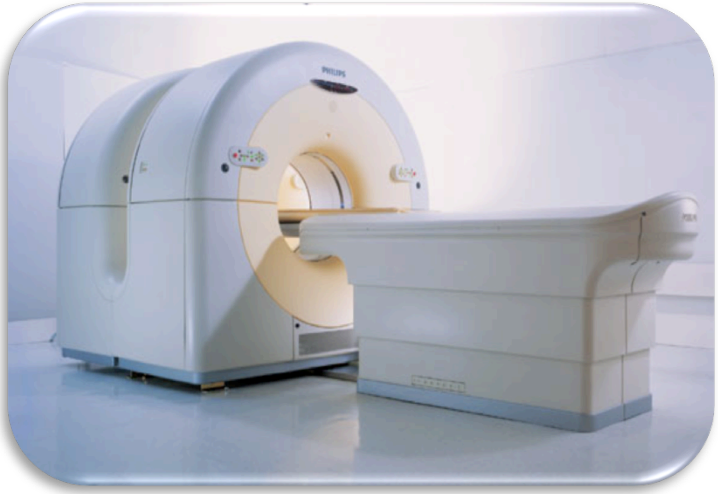
II. PET/CT Scanners

Basic PET/CT Architecture



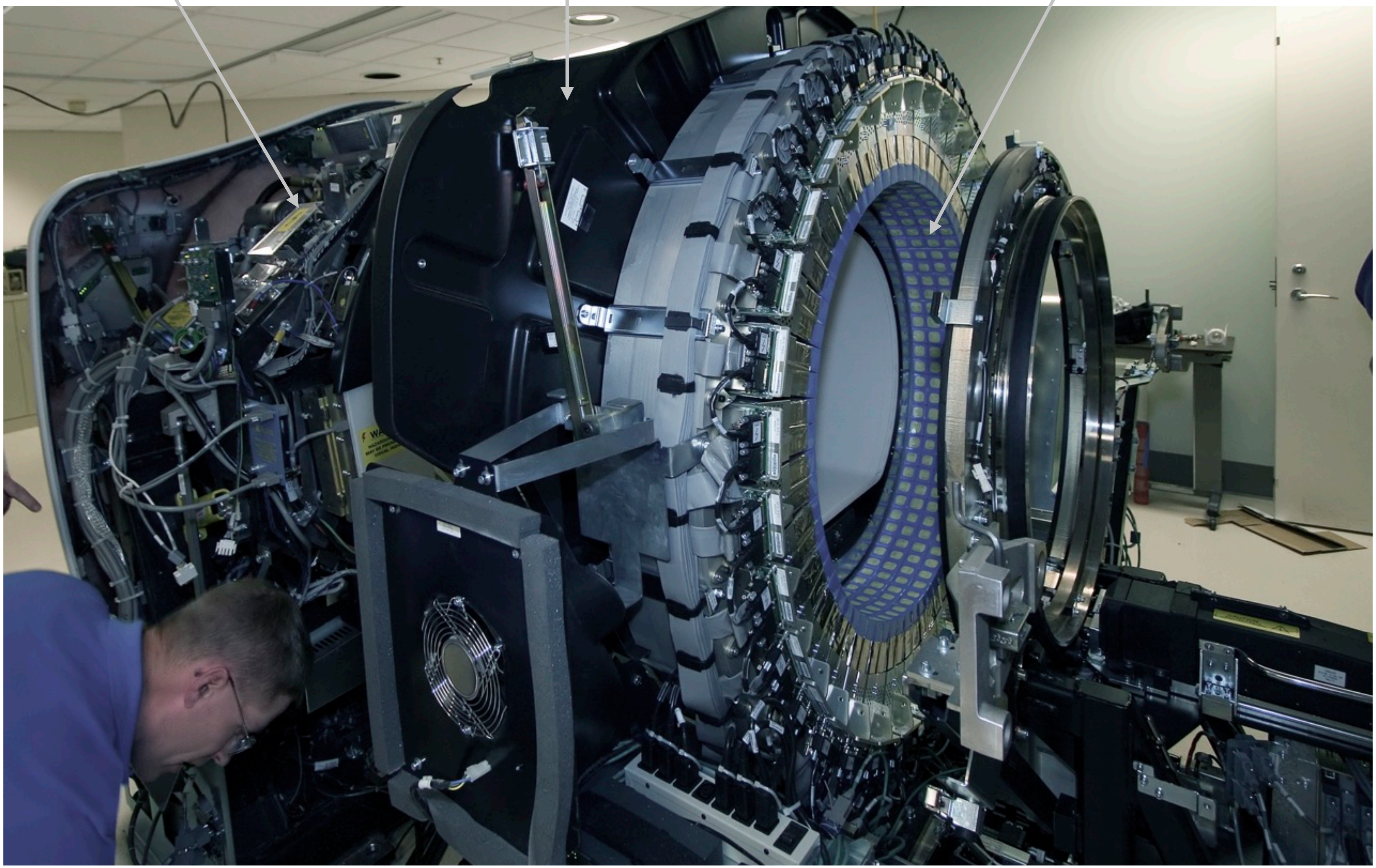
PET/CT Scanners

Clinical PET/CT

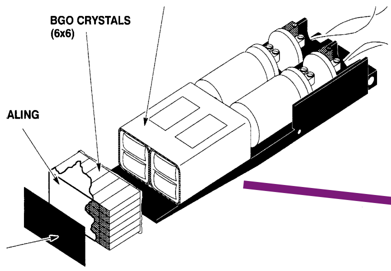


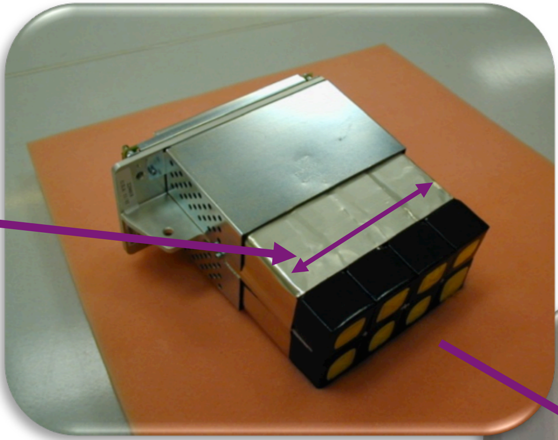
Micro PET/CT

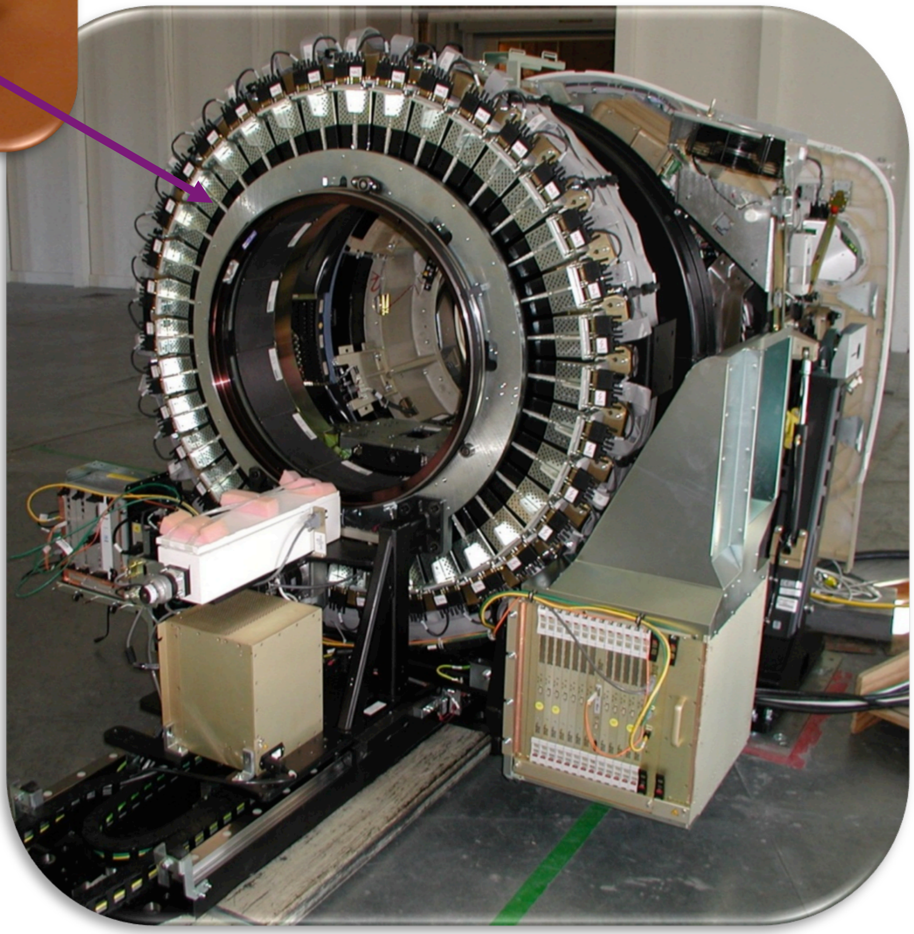
Commercial/Clinical PET/CT Scanner



Inside Typical PET scanner





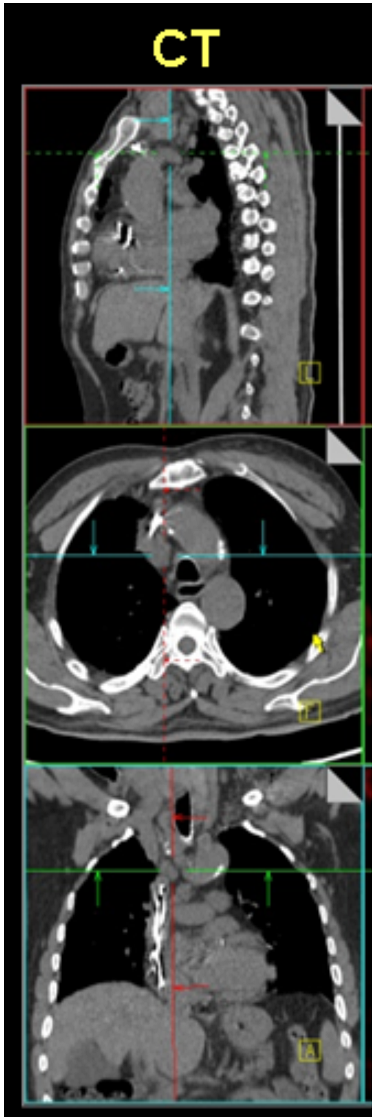


Block matrix: BGO crystals
- 6 x 8 crystals (axial by transaxial)
- Each crystal:
  - 6.3 mm axial
  - 4.7 mm transaxial

Scanner construction
- Axial:
  - 4 blocks axially = 24 rings
  - 15.7 cm axial extent
- Transaxial:
  - 70 blocks around = 560 crystals
  - 88 cm BGO ring diameter
  - 70 cm patient port

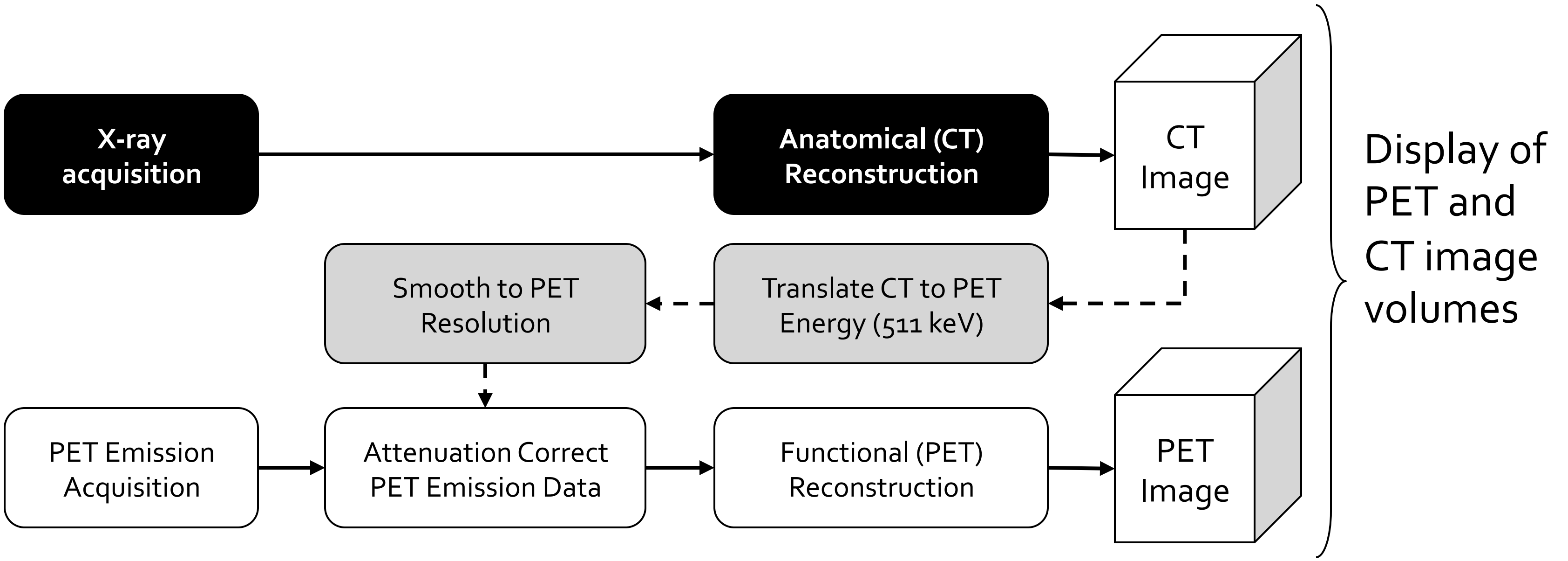
13,440 individual crystals

Power of PET + CT



PET/CT Scanner Operation

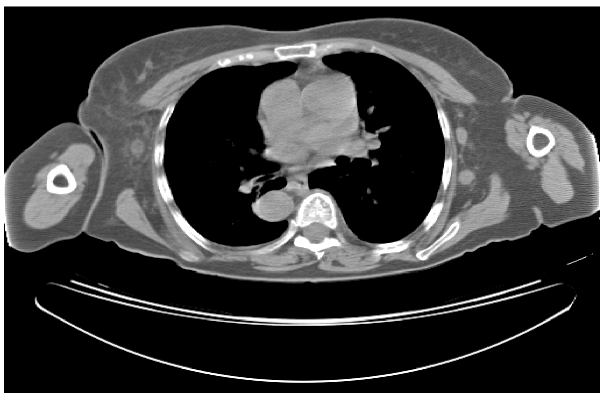
- CT images are also used for attenuation correction of the PET data

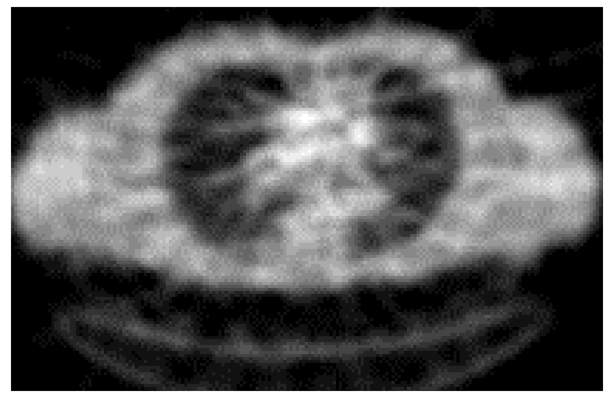


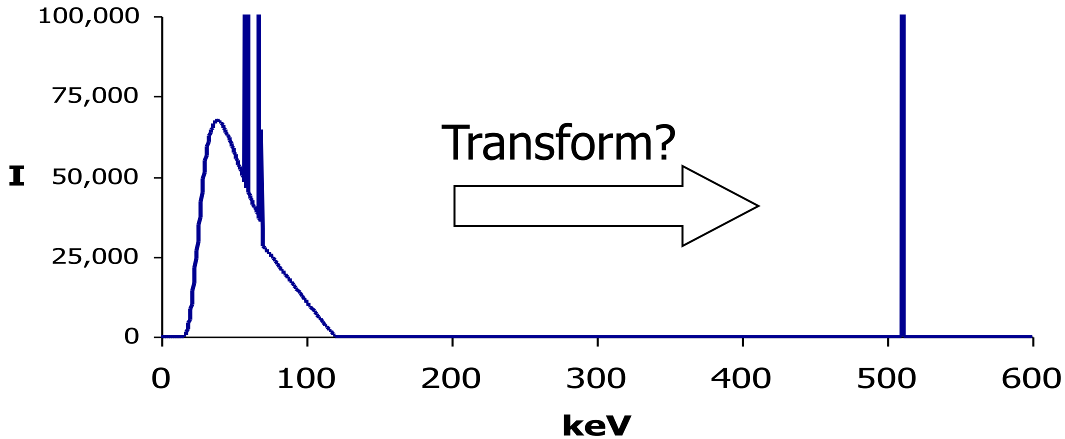
- Note that images are not really fused, but are displayed as fused or side-by-side with linked cursors

X-ray and Annihilation Photon Transmission Imaging for Attenuation Correction

X-ray (~30-120 keV)	**PET Transmission** (511 keV)
Low noise	Noisy
Fast	Slow
Potential for bias when scaled to 511 keV	Quantitatively accurate for 511 keV

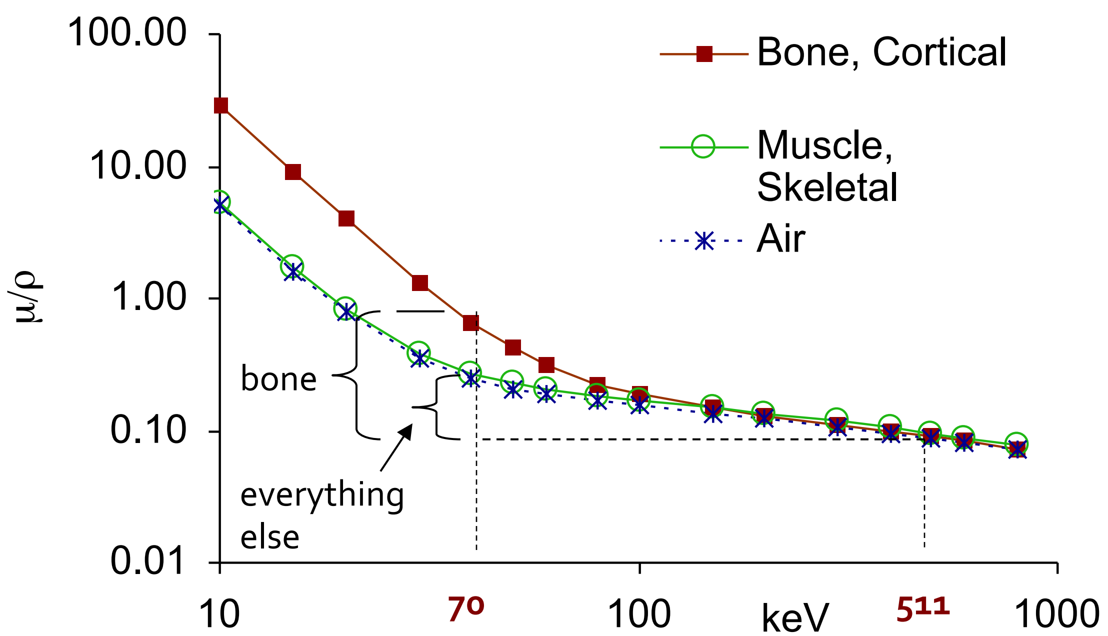






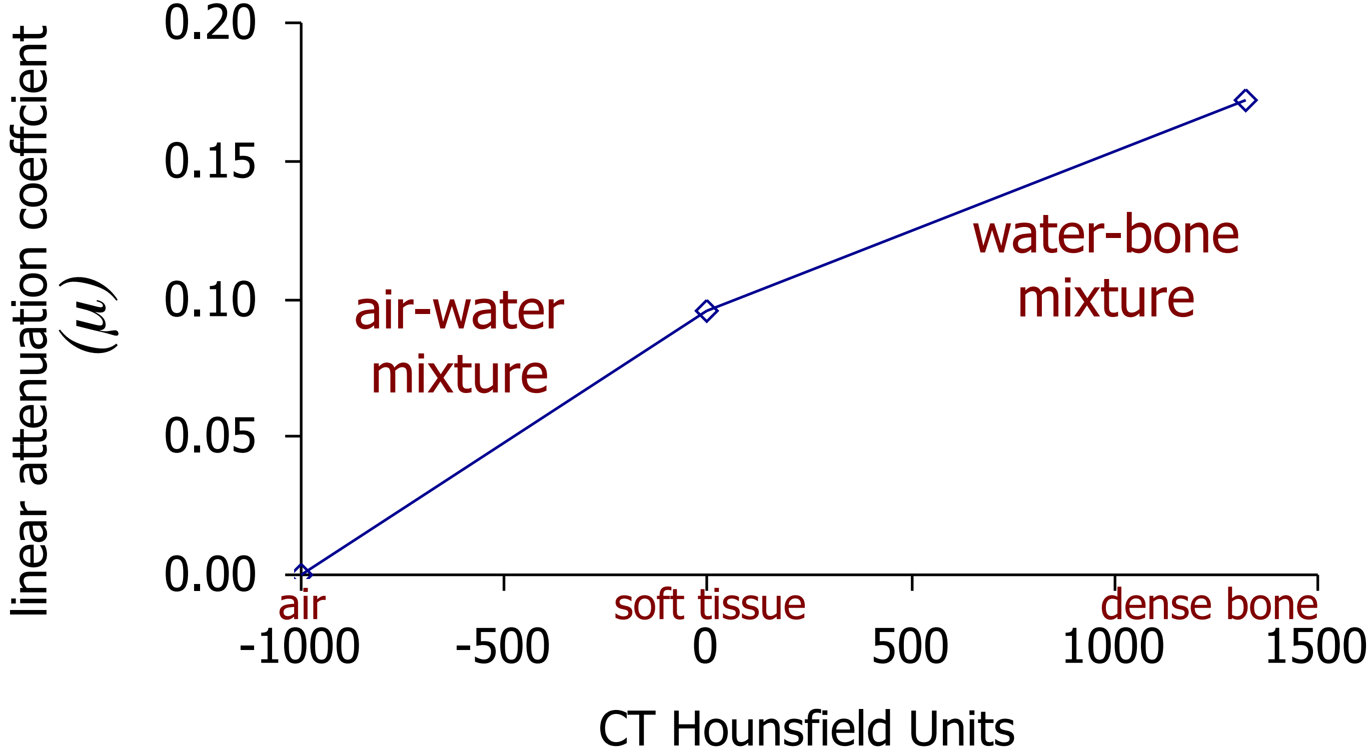
CT-based Attenuation Correction

- The mass-attenuation coefficient (μ/ρ) is similar for all non-bone materials since Compton scatter dominates for these materials
- Bone has a higher photoelectric absorption cross-section due to presence of calcium
- Can use two different scaling factors: one for bone and one for everything else

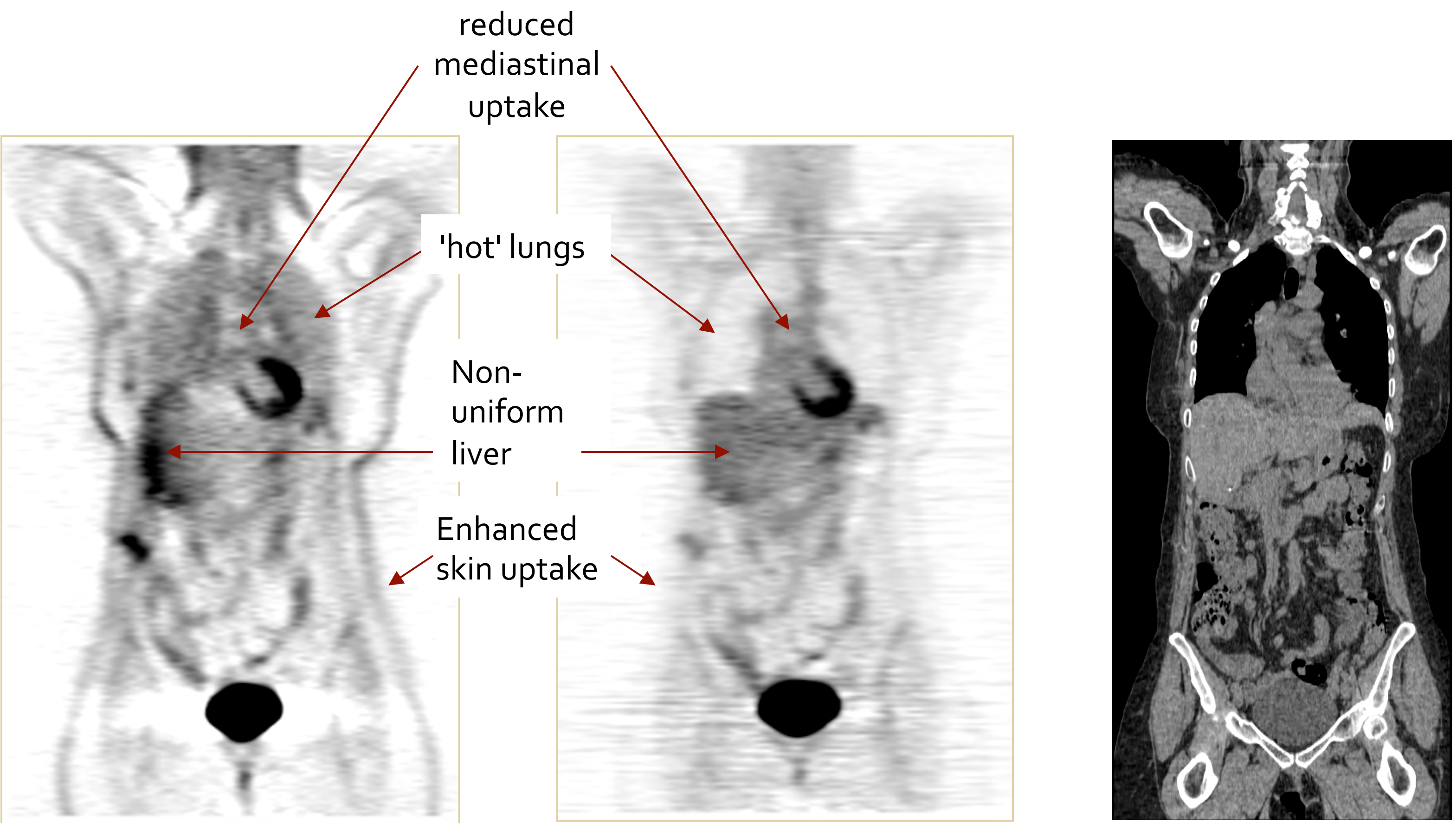


CT-based Attenuation Correction

- Bi-linear scaling methods apply different scale factors for bone and non-bone materials
- Should be calibrated for every CT scanner setting
  - X-ray energy spectrum (kVp)
  - Presence/absence contrast agents



Effects of Attenuation: Patient Study



PET: without attenuation correction

PET: with attenuation correction (accurate)

CT image (accurate)

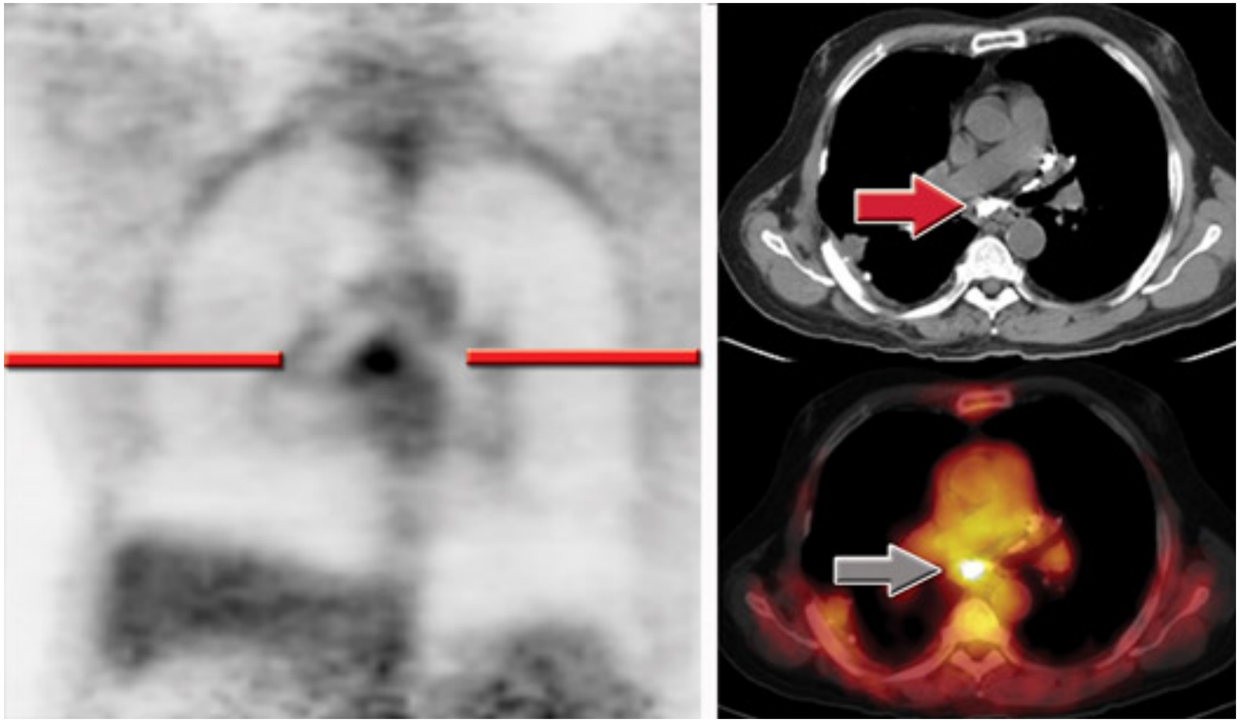
Material artifact: Metal Clip

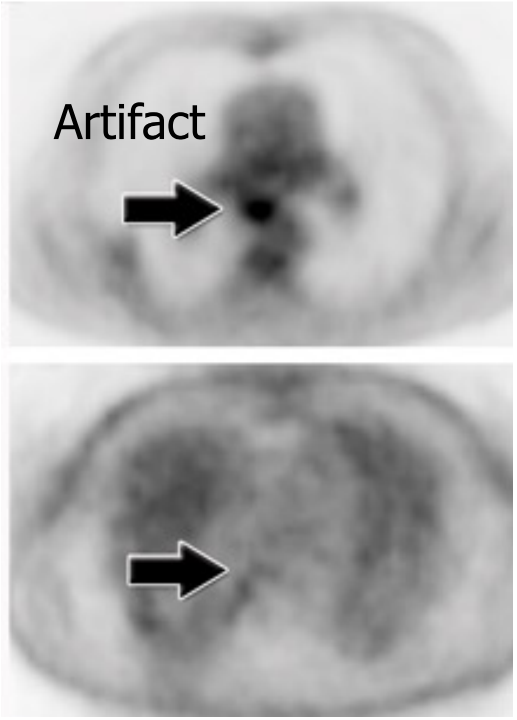
Artifact

CT PET with CTAC

Courtesy O Mawlawi MDACC

Material artifact: Calcified Lymph Node



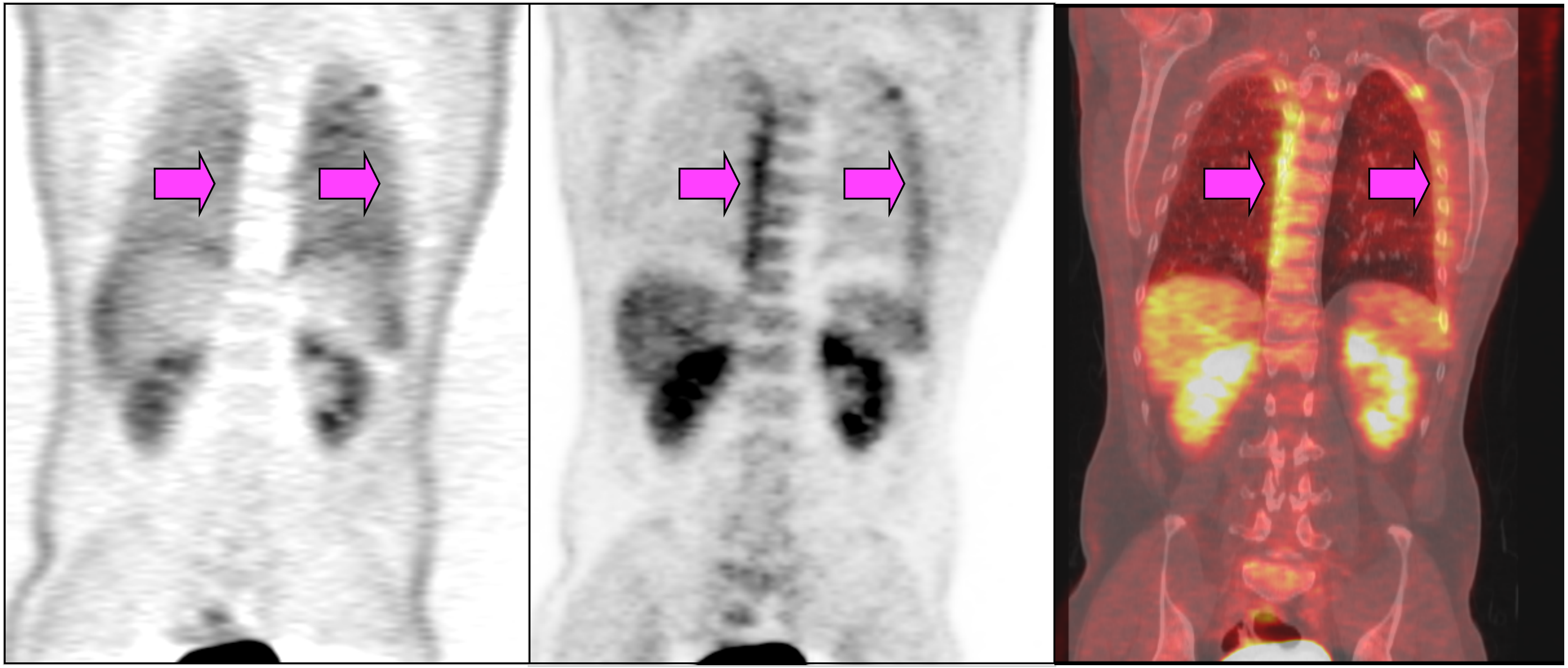


Non-AC PET

Courtesy T Blodgett UPMC

Positional artifact: Patient and/or bed shifting

- Large change in attenuation at lung boundaries, so very susceptible to errors

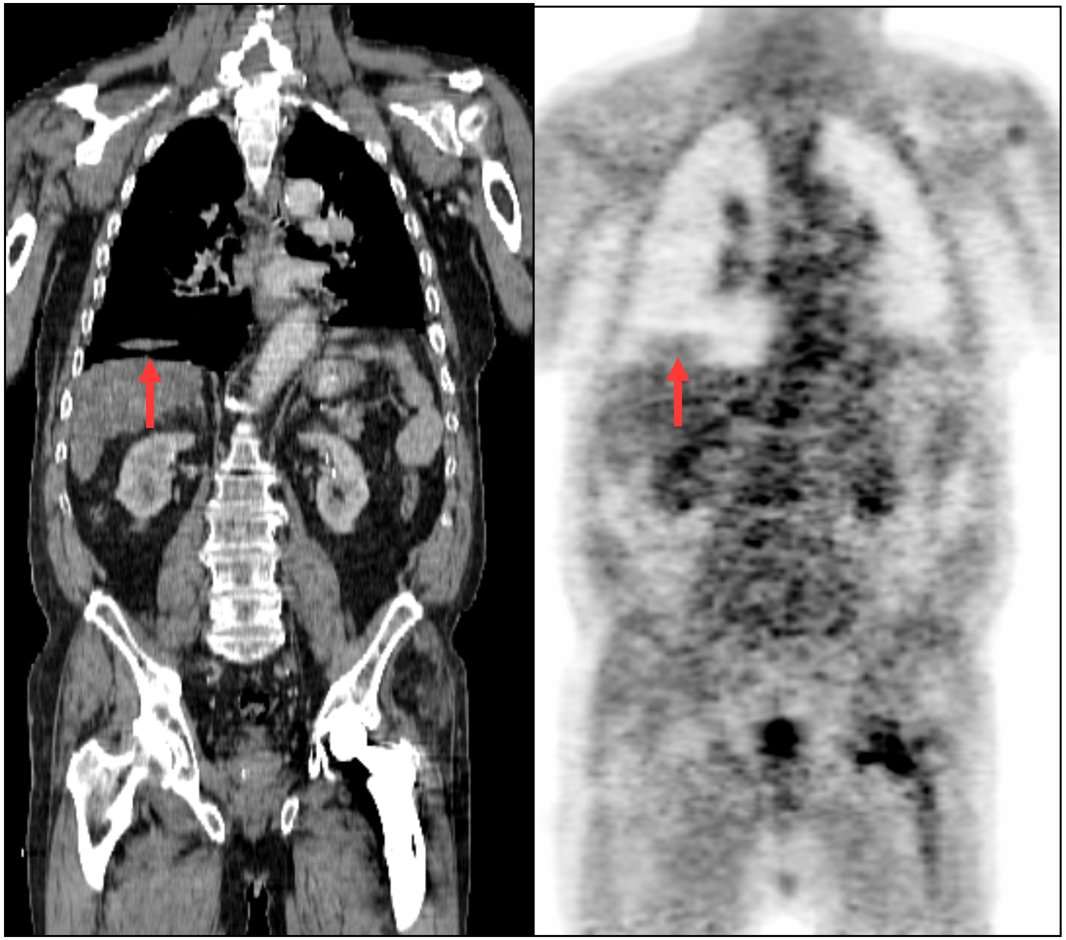


PET image without attenuation correction

PET image with CT-based attenuation correction (used for measuring SUVs)

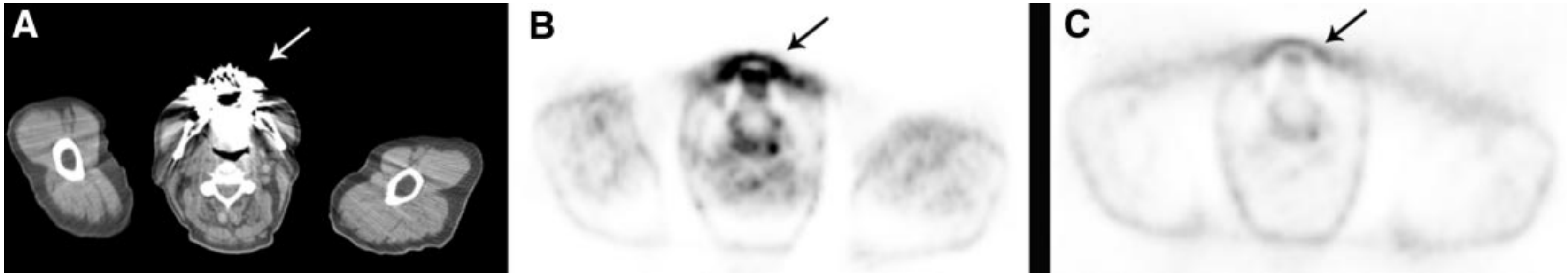
PET image fused with CT

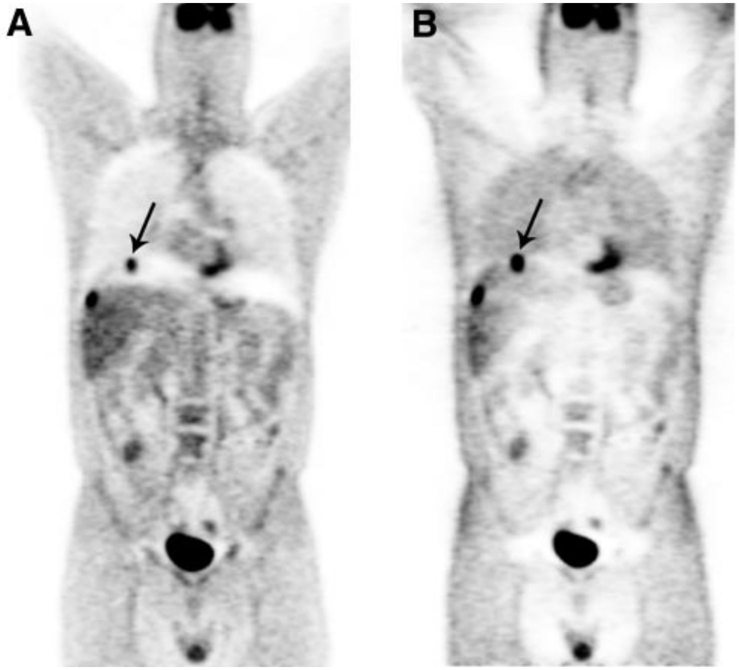
Breathing Artifacts: CT-based attenuation correction



Attenuation artifacts can dominate true tracer uptake values

Clinical Impact Attenuation Correction





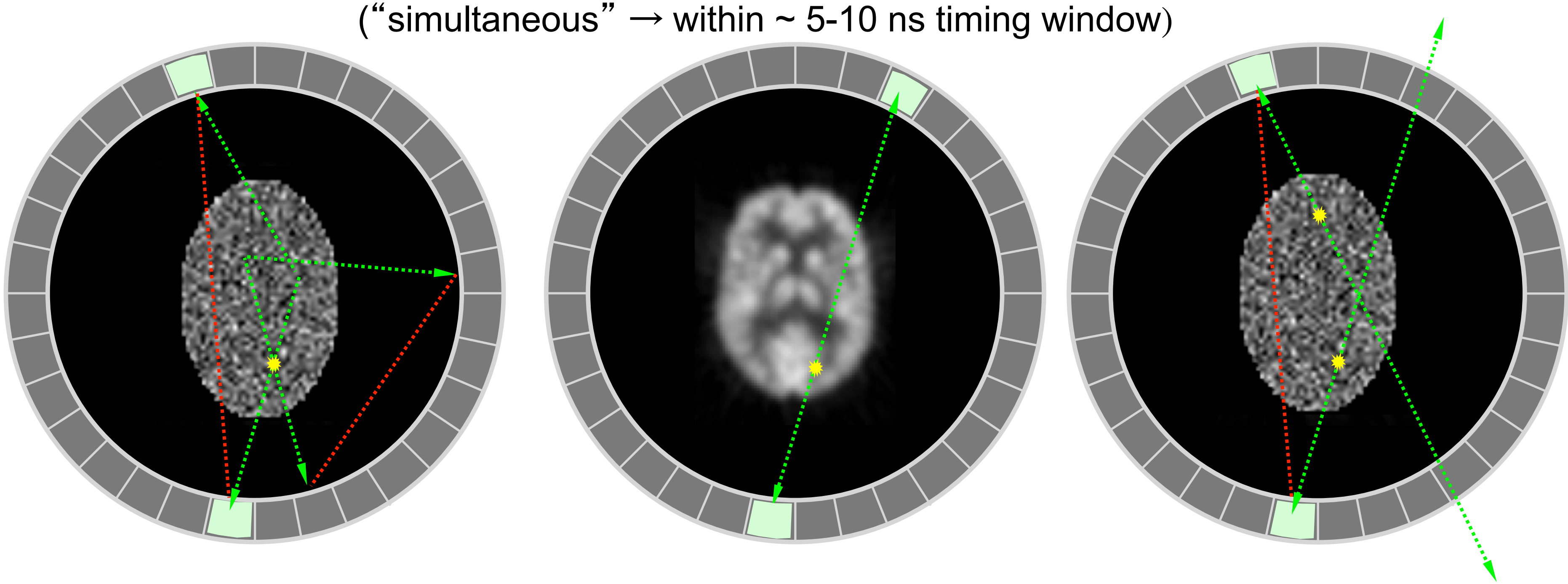
Mawlawi 2012

- How do we remove these artifacts due to poor attenuation correction?

III. PET/CT Imaging Uncertainties

PET Signal and Noise

PET detectors seek simultaneous gamma ray absorptions
("simultaneous" → within ~ 5-10 ns timing window)



Scattered coincidence:
one or both photons change direction from a scatter before detection

True coincidence:
anti-parallel photons travel directly to and are absorbed by detectors

Random coincidence:
photons from different nuclear decays are detected simultaneously

Question: what happens to SNR if we increase the timing window?

PET signal components

$$P = T + S + R$$

Measured Projections	True Signal	Noise from Scatter	Noise from Random

$$T \propto \Delta t \cdot r_{ij} \propto activity$$

r_{ij} = photon pair detection rate in detector pixels i,j

$$R \propto \Delta t \cdot r_i \cdot r_j \propto activity^2$$

r_i = single photon detection rate in pixel i

- S and R has to be estimated and removed

- Estimation challenges
  - R estimation accurate and efficient (singles method)
  - S estimation can have significant errors from tissue heterogeneity

Signal and Noise Estimates

Scatter Fraction (SF)

$$SF = \frac{S}{T+S}$$

Signal to Noise Ratio (SNR)

$$SNR = \frac{T}{\sigma(P)} \approx \frac{T}{\sqrt{T+S+\alpha R}}$$

α depends on randoms estimation method

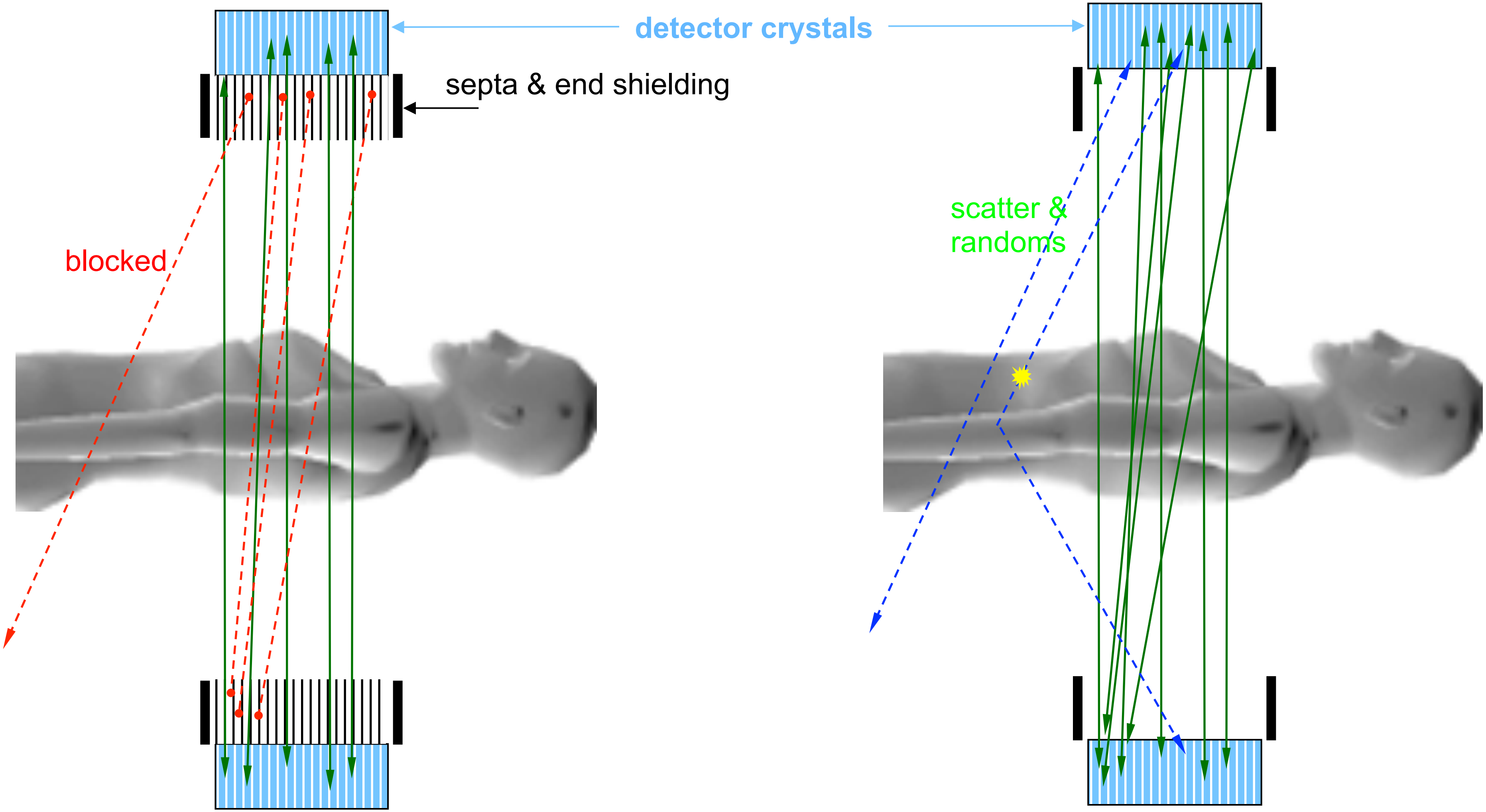
Noise Equivalent Counts (NEC)

$$NEC = \frac{T^2}{T+S+\alpha R}$$

PET Acquisition: 2D vs. 3D Mode

Form of collimation (septa) that separate axial slices in 2D PET

- reduces scattered and random events (also reduces trues!)



2D PET uses axial septa

3D PET uses no septa

PET Spatial Resolution

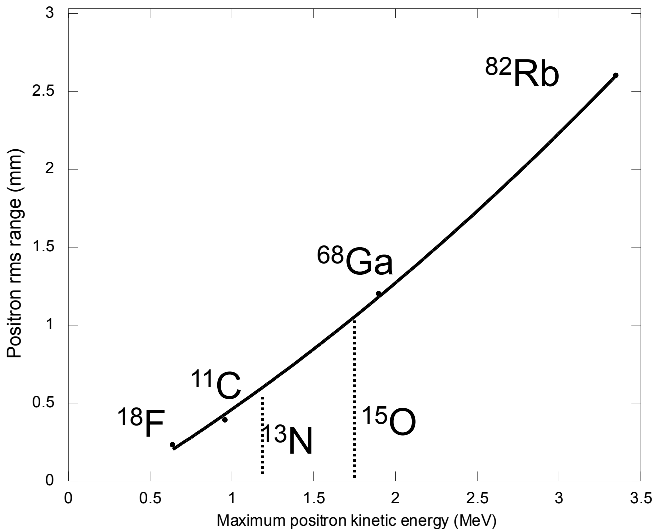
- Positron Physics
  - Positron Range
  - Photon Non-colinearity
- Detectors
  - Response function
- Ring Geometry
  - Non-uniform LOR sampling
  - Depth-of-interaction
- Reconstruction Filters

Resolution components add in quadrature

$$R_{system} = \sqrt{R^2_{pos.phys.} + R^2_{\det} + R^2_{sampl} + R^2_{recon}}$$

Positron Emission Physical Limits

- **Positron range**
  - maximum energy of isotope
  - scatter medium



data from Derenzo, et al. IEEE TNS 33:565-569, 1986

- **Photon non-colinearity**
  - Non-colinearity: $R_{\text{non-colin}}$ = 0.0022 x Ring Diameter
  - Clinical scanner: Diam. ~ 80 - 90 cm; $R_{\text{non-col.}}$ ~ 2 mm
  - Small animal scanner ~ 15 - 20 cm; $R_{\text{non-col.}}$ ~ 0.4 mm

PET Ring Geometry Effect on Resolution

Data Sampling Error:

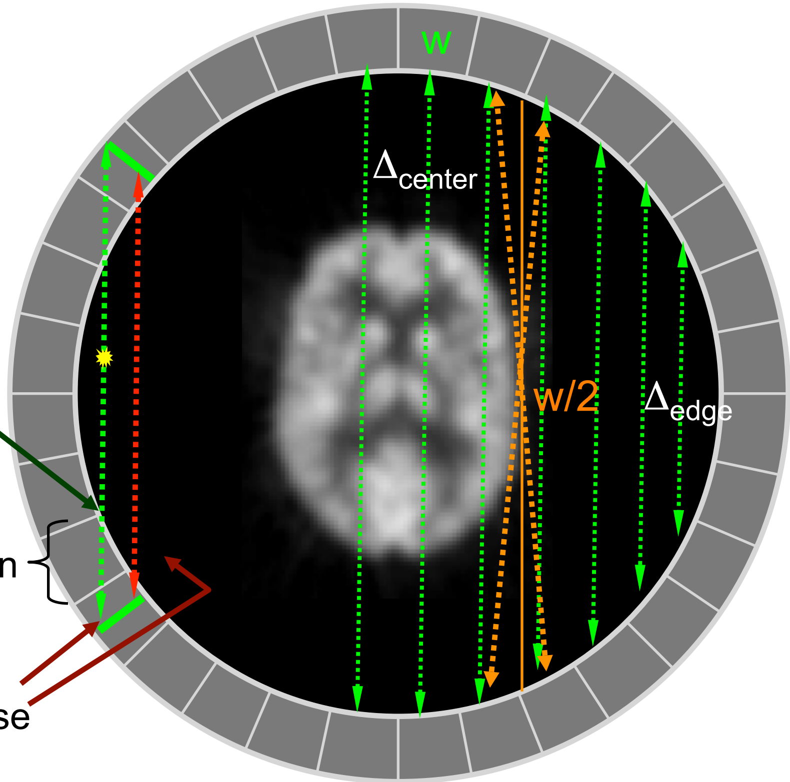
- Coincidence lines-of-response are not uniformly spaced across a ring detector
- Interpolate to uniform spacing, or account for non-uniformity in reconstruction

Depth-of-Interaction error:

entrance position and true line-of-response

photon penetration

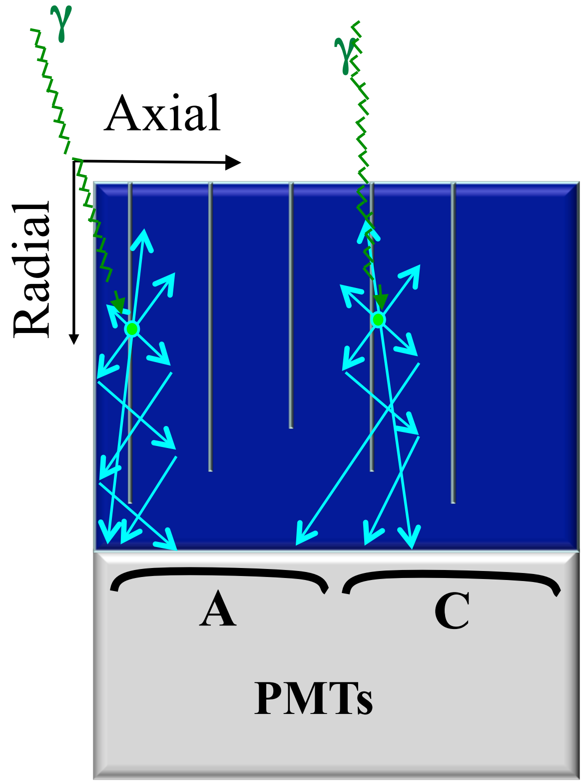
detection position and assigned line-of-response



Detector Signal Decoding

Light Sharing

Relative PMTs signal heights depend on crystal of interaction



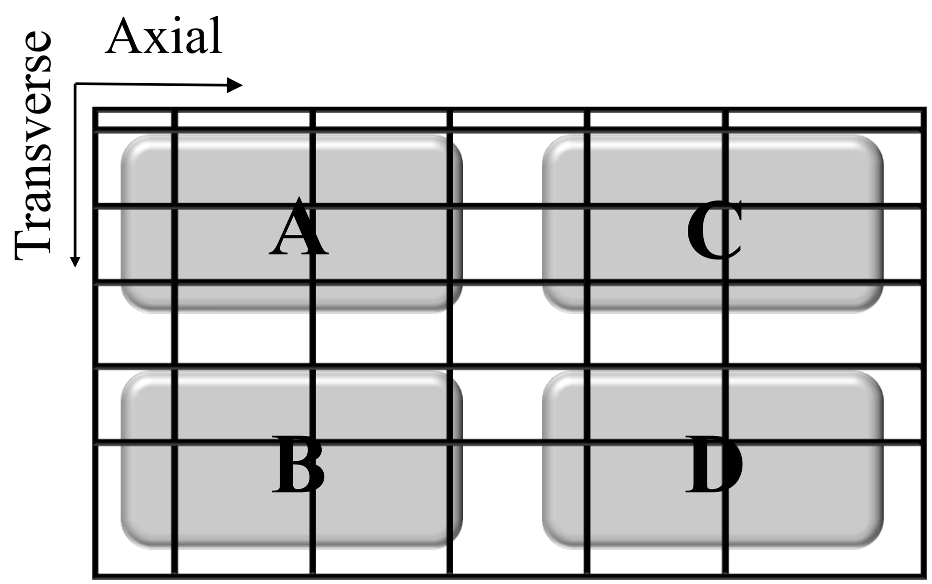
Signal Decoding

Energy, E = A + B + C + D

Axial position, Z = (C +D) / E

Transverse position, X = (B + D) / E

Radial position: not determined (no DOI)



PET Sensitivity Factors

1. **Absorption efficiency of detectors**
   – scintillation crystal attenuation coefficient
   – scintillation crystal thickness
   – detector response uniformity

2. **Solid angle coverage of object by detectors**
   – PET ring diameter
     <u>smaller diameter</u>
     + increases solid angle and sensitivity, *reduces* system cost
     - leads to DOI resolution degradation
     - limits patient size
   – PET ring axial length
     <u>larger axial extent</u>
     + increases solid angle and sensitivity
     - increases system cost

Detector Sensitivity vs. Resolution Tradeoff

Inorganic scintillation crystals

Property	NaI(Tl)	BGO	LSO(Ce)	BaF_2	relevant <u>PET scanner property</u>
Density (gm/cm^3)	3.67	7.13	7.40	4.89	sensitivity
Effective Atomic Number	50	74	66	54	sensitivity
Attenuation coefficient, μ, (@511keV, 1/cm)	0.34	0.95	0.88	0.44	sensitivity
Coincidence efficiency $(1-e^{-\mu t})^2$, t = tickness (cm)*	41% t=3	89% t=3	69% t=2	54% t=3	sensitivity
Light Output (photons/keV)	38	8	20-30	10	energy & spatial resolution
Decay Time (ns)	230	300	40	0.8, 620	counting speed (randoms rate, dead-time
Wavelength (nm)	415	480	430	225, 310	photo-sensor matching, manufacturing cost
Index of Refraction	1.85	2.15	1.85	1.56	photo-sensor matching, manufacturing cost
Hygroscopy	yes	no	no	no	photo-sensor matching, manufacturing cost

*crystal thickness, t: typically BGO scanners use t = 3cm, LSO scanners use t = 2cm for cost reasons. PET scanners are not made from NaI(Tl) or BaF_2 due to low sensitivity, despite other advantages

Geometric Efficiency vs. Sensitivity

PET scanner **sensitivity** scales with the number of **detectable coincidence events**, which in turn scales as θ_{max}.

This results in lower sensitivity at the end of any PET scanner

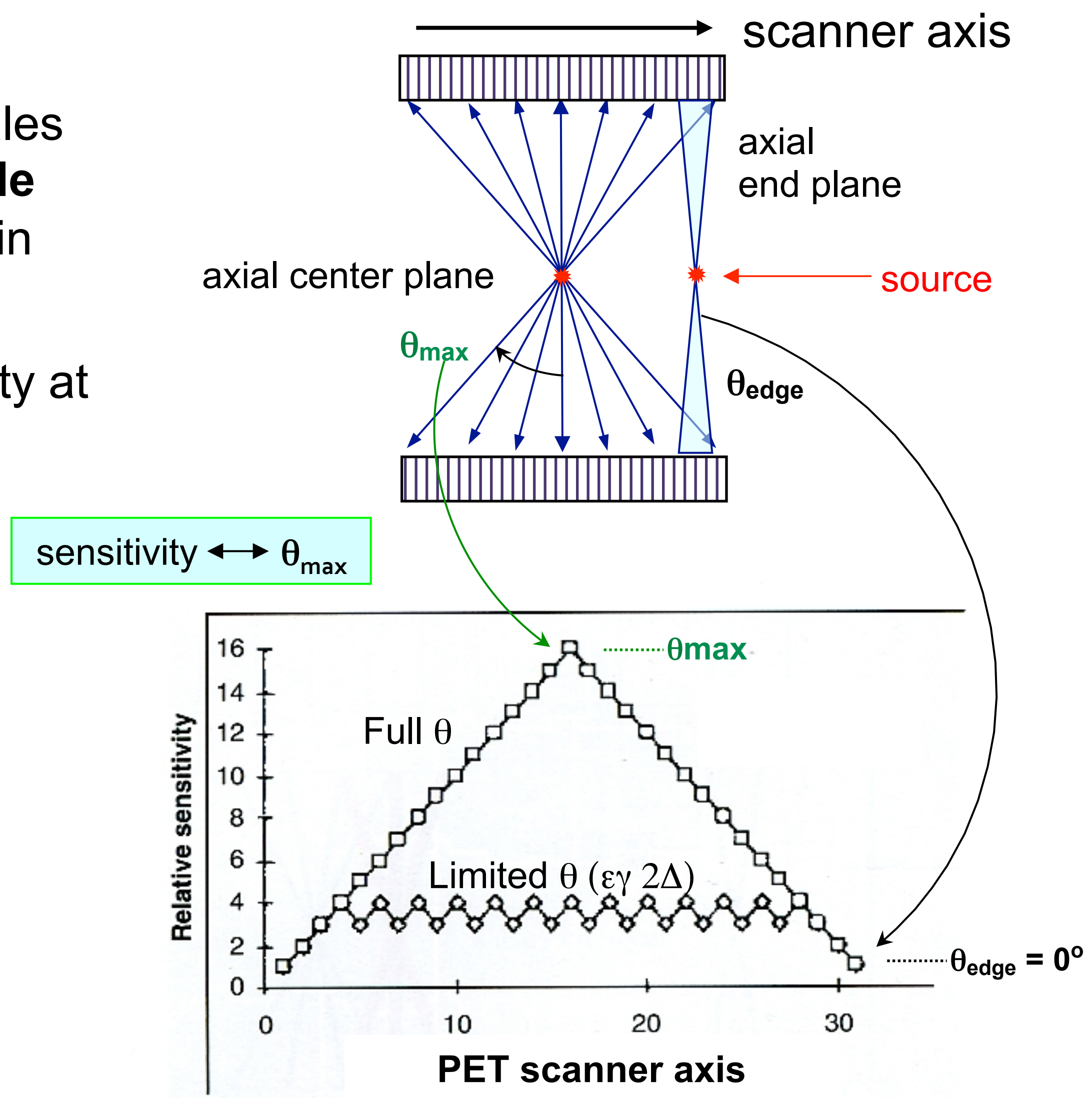


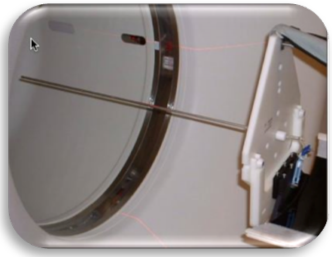
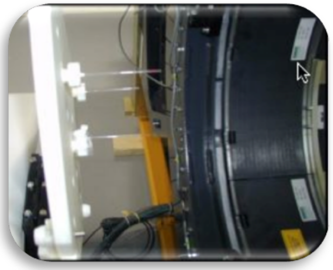
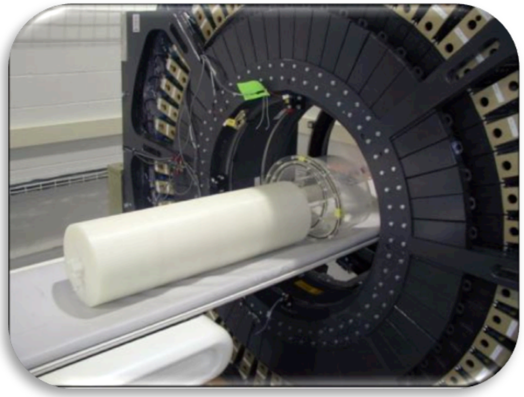
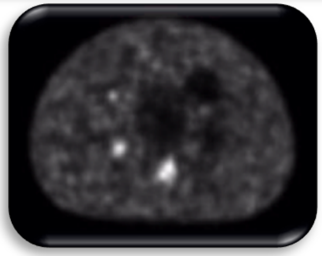
FIGURE 10 Comparison between 2D (axial collimation in place) and 3D (axial collimation removed) sensitivity.

Graph from “Emission Tomography”, Eds. Wernick, Aarsvold, pg.186

QA for PET Scanners: Evaluation of Performance Metrics

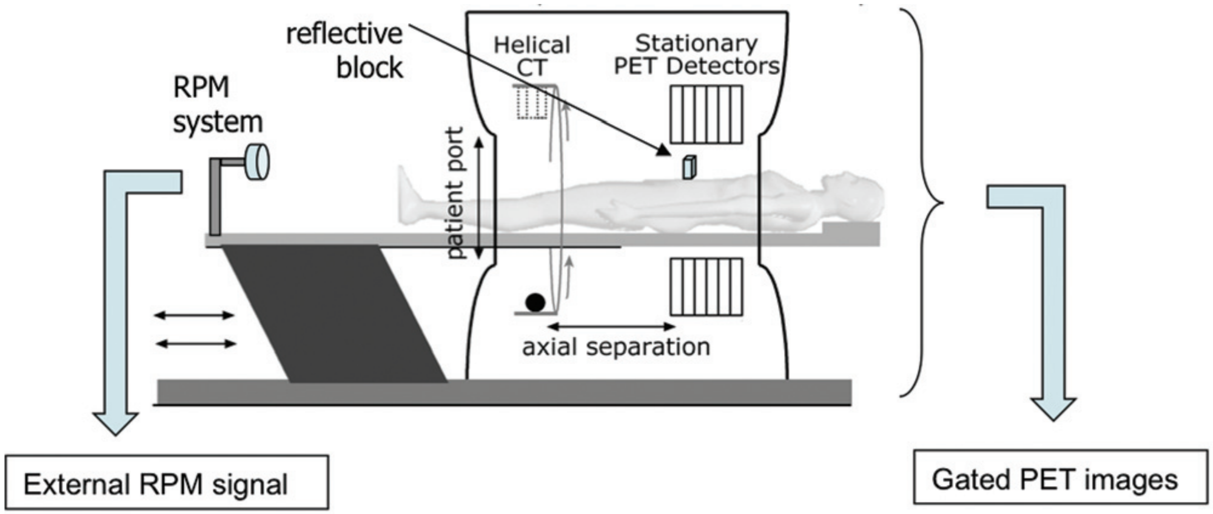
Current specifications based on National Electrical Manufacturers Association (NEMA) Standard

- Sensitivity - both system and per transaxial slice (measured with a line source)
- Spatial resolution - measured with a point source and an analytical image reconstruction algorithm at several positions in the scanner FOV (x,y,z resolution)
- Uniformity - measured with a uniform cylinder of activity
- Count rate - measured with a decaying line source in a solid, cold cylinder
- Dead time correction accuracy - measured from the count rate data
- Scatter fraction - measured from the count rate data
- Attenuation correction accuracy, contrast performance - from a non-cylindrical phantom with hot and cold spheres.

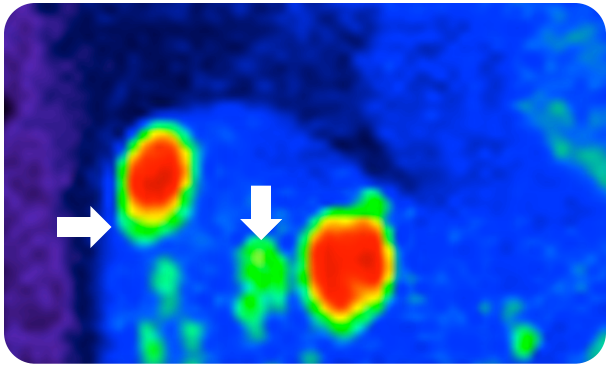
IV. Advances & applications

Respiratory-gated PET and PET/CT



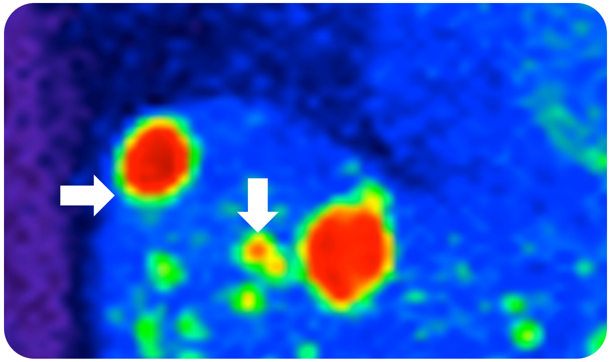
(Liu 2010)

Static PET



$SUV_{max} = 9.5$

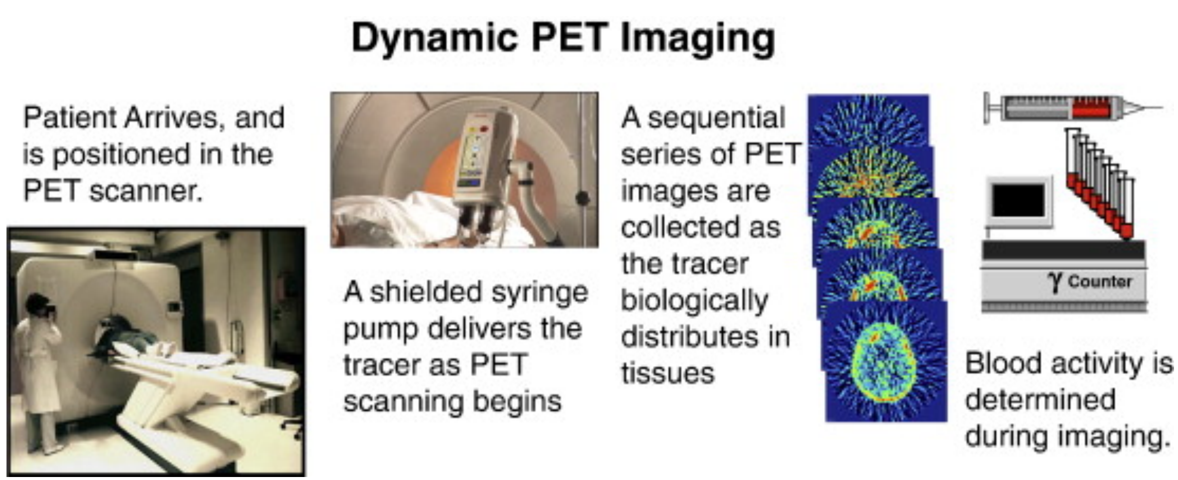
Gated PET



$SUV_{max} = 15.3$

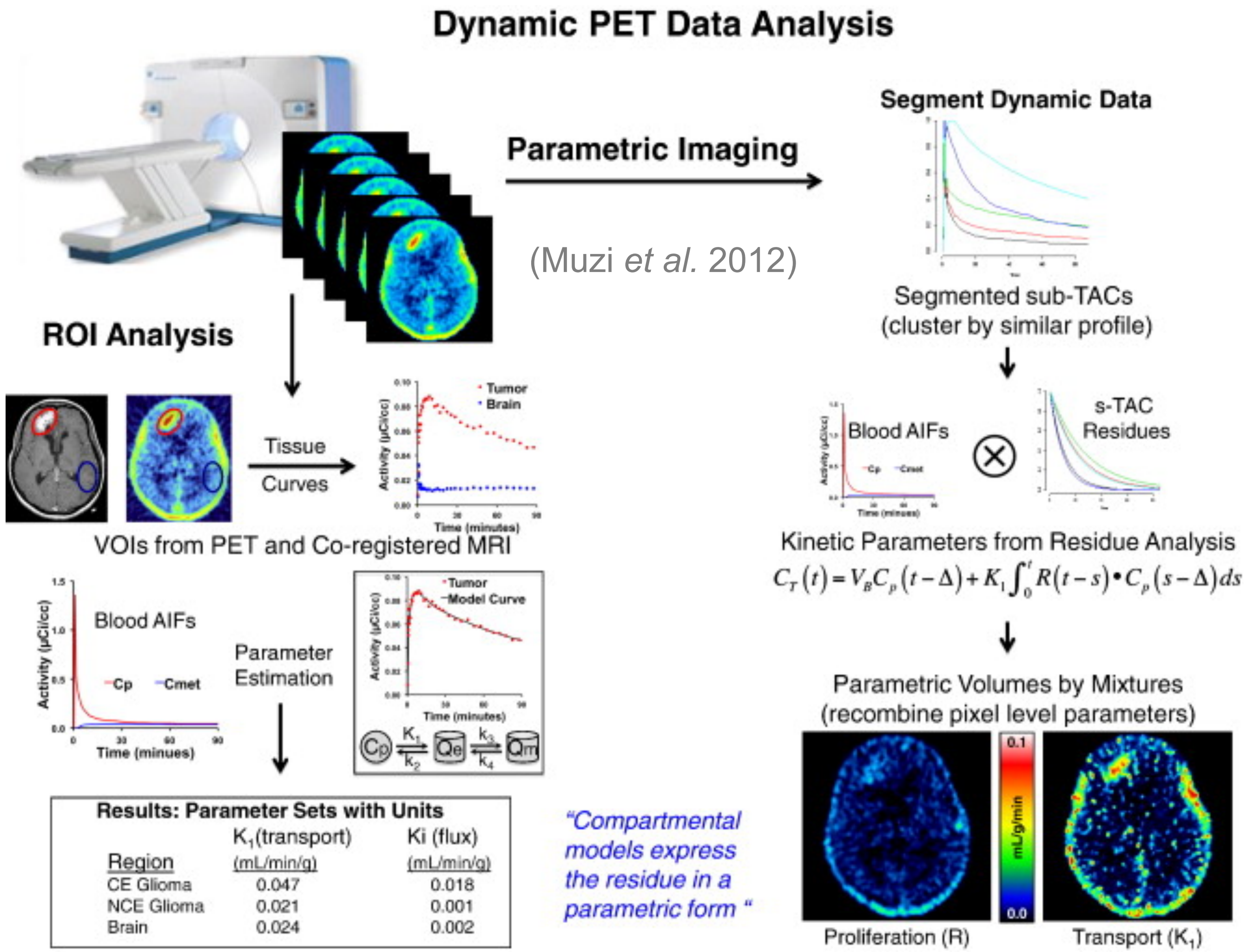
PET Acquisition: Static vs. Dynamic

- Static PET
  - Time-averaged image frame from all detected events at a given bed position
- Dynamic PET
  - Time-binned image over multiple frames at a given bed position



(Muzi *et al.* 2012)

Quantitative Dynamic PET



Results: Parameter Sets with Units

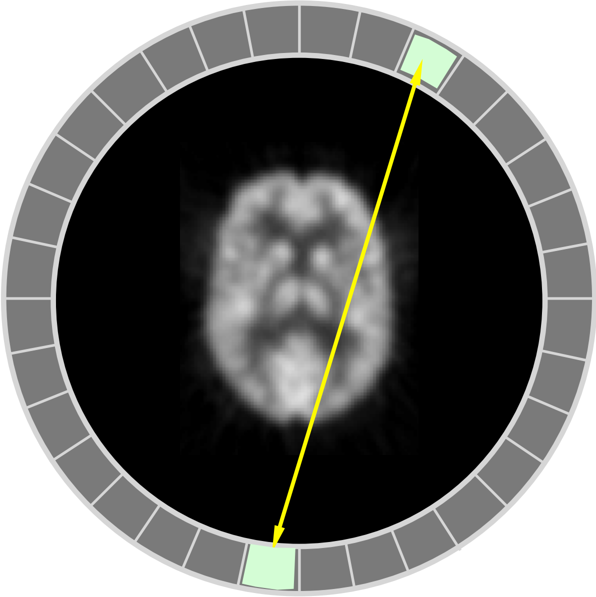
Region	K_1(transport) (mL/min/g)	Ki (flux) (mL/min/g)
CE Glioma	0.047	0.018
NCE Glioma	0.021	0.001
Brain	0.024	0.002

- Kinetic model of dynamic PET is tracer specific

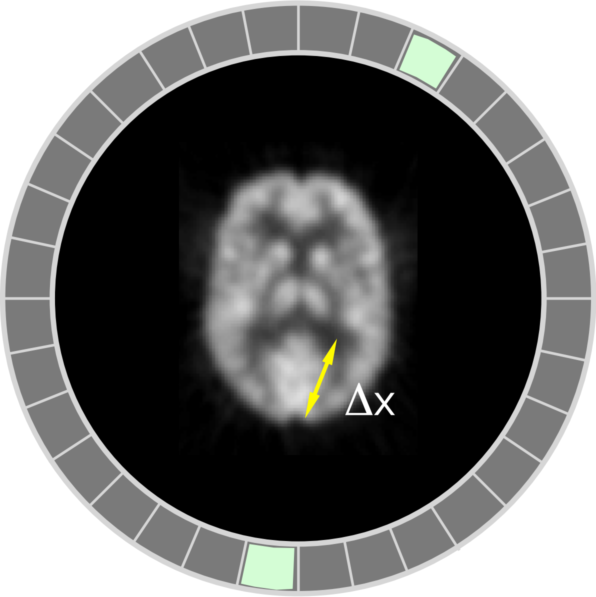
Modern Times: Time-of-Flight

- Time-of-flight capability is now offered in many new PET scanners
  - Measure time difference of detection of coincidence gammas
  - Defines a line segment in space, shorter than distance between detectors
  - Improves image signal to noise that is a function of the object size.

Conventional LOR



TOF Gaussian SOR



segment length

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

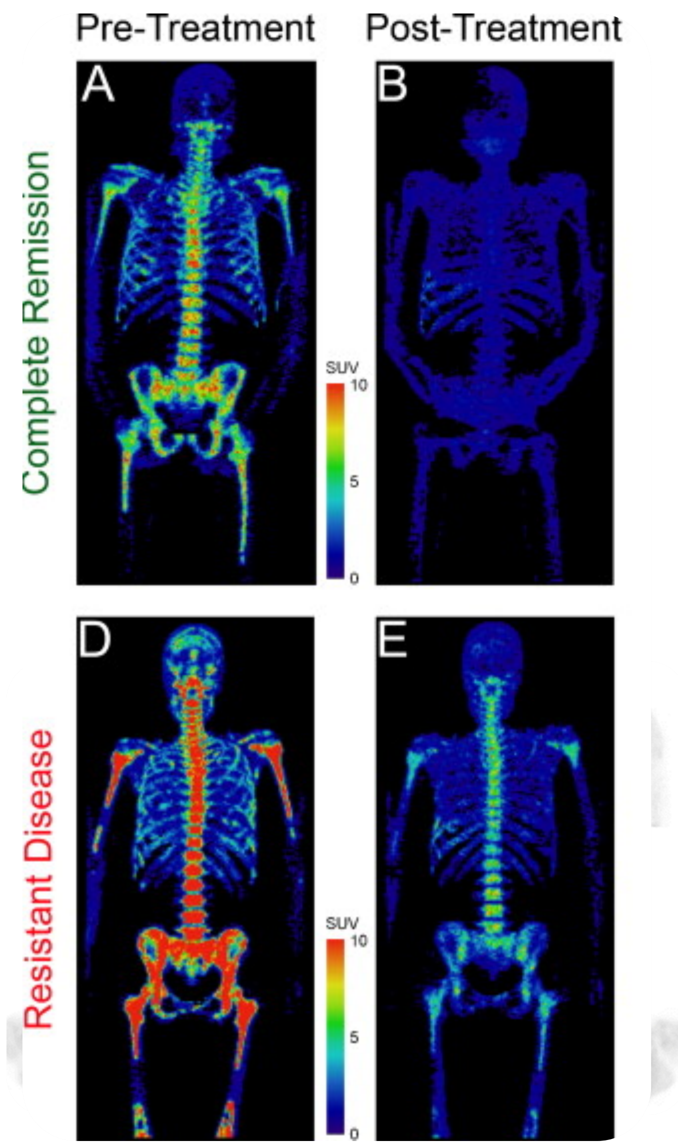
c = speed of light

Δt = timing resolution

Δx = 7.5 cm for the Δt ~ 0.5 ns typical of TOF PET scanners

PET Clinical Applications

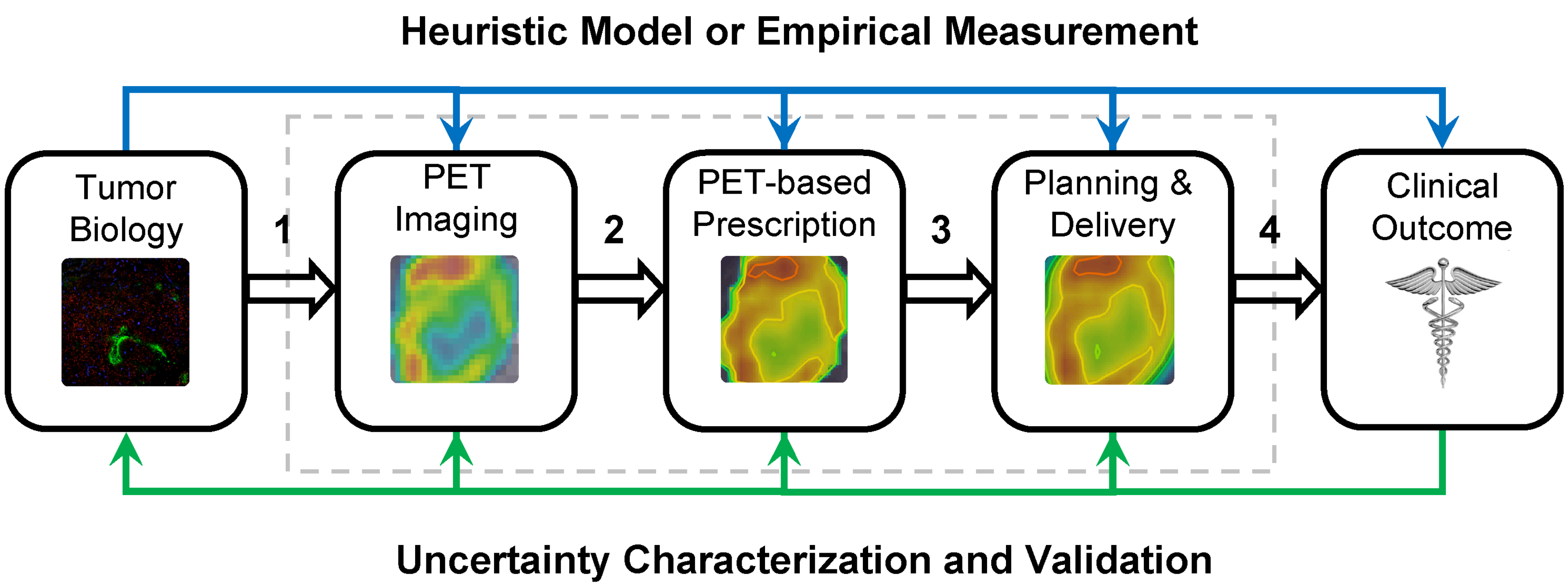
- **Diagnosis and staging**
  - FDG PET alters staging in at least 30 % of cancer patients
- **Target definition**
  - PET/CT-based targets more conformal to surgically resected tumor volumes
  - Reduces inter-observer variation
  - RTOG recommend NSCLC
    CTV = GTV + PET-positive nodes
- **Treatment response assessment**
  - PET response precedes CT and MRI response
  - Early response prognostic of clinical outcome



(Vandenhoek 2011) (Hatt 2012)

Future: PET/CT-guided Radiotherapy

- Biologically conformal radiotherapy / Dose painting
  - Biological target volumes (BTV) for simultaneous integrated dose boosts (Ling 2000, Tome 2003, Madani 2009)
- Dose painting by numbers accounts for intratumoral variations in response to therapy (Bentzen 2005)



(Bowen 2011)

PET Introduction Summary

- **Concept**
  - Physics of positron emission, annihilation photons, coincidence detection
- **Components**
  - 2D collimated vs. 3D acquisition mode, detector block
- **Spatial resolution**
  - Positron range, detector response, line-of-response sampling, depth-of-interaction
  - **Take home 1: clinical PET resolution ~ 5 mm, small animal PET ~ 1 mm**
- **Quantitation**
  - CT attenuation correction
  - **Take home 2: separable attenuation correction makes PET more quantitative than SPECT or MRI**
- **Sensitivity**
  - Absorption efficiency, geometric efficiency
  - **Take home 3: PET sensitivity 10^3 greater than SPECT, 10^6 greater than MRI**
- **Image formation**
  - Acquisition
  - Reconstruction

IV. Q & A

Question 1

- How do PET and SPECT compare in terms of…
  - spatial resolution?
  - quantitative accuracy?

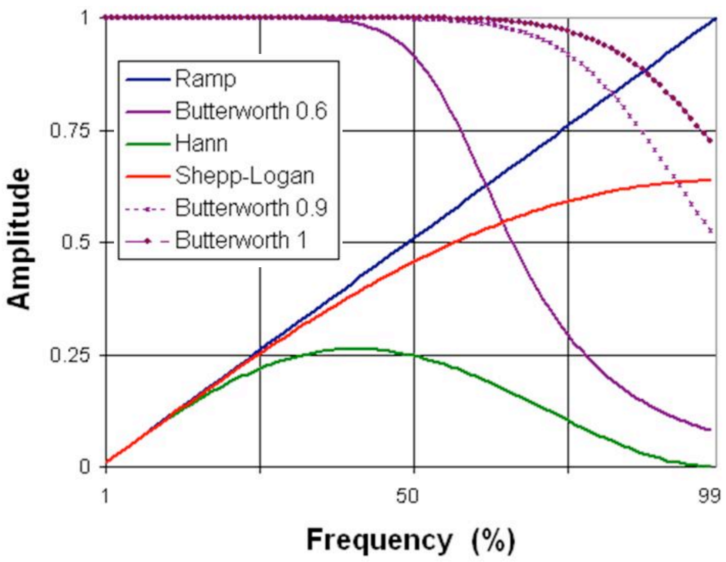
  - PET has higher spatial resolution, despite disadvantage of finite positron range prior to photon emission, because less attenuation/scatter of 511 keV in tissue compared to lower SPECT photon energies

  - PET has higher quantitative accuracy due to simpler separable attenuation correction that enables absolute estimation of activity concentration

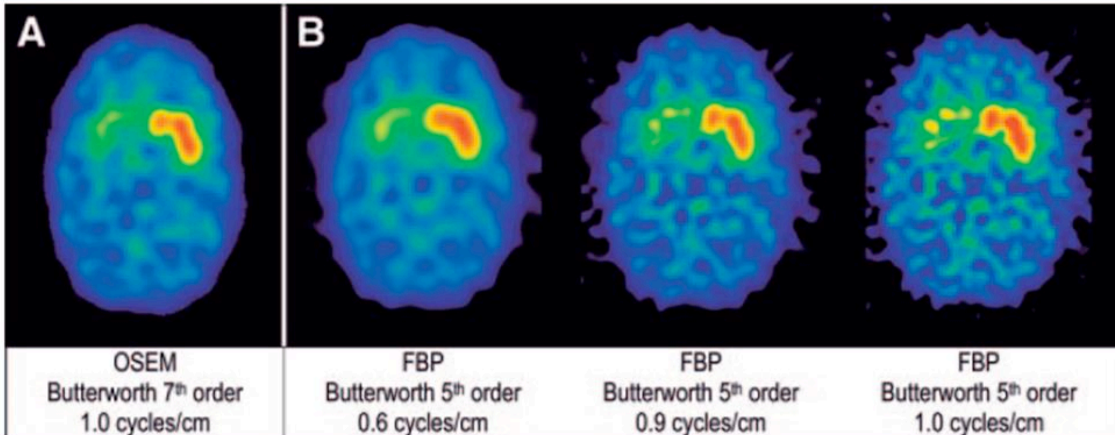
Question 2

- What is purpose of different filters?
- Who chooses filter?

Modified Frequency Filters



Effect of Butterworth-filter cutoff



Question 3

- SPECT lecture slide on imaging equation stated "Ignore inverse-square dependence of fluence”. How can inverse square be ignored when activity at any distance from a source is heavily effected by the inverse square law?

- Approximation is based on distributed activity sources whose photon emission lines can be rebinned into parallel projections, leading to tomographic image reconstruction

Question 4

- What is future of ^{99m}Tc SPECT for bone imaging given worldwide decreasing supply of depleted uranium for generator-based production? Will PET be cheaper option?

- [^{18}F]NaF PET for bone imaging is gaining prominence for both quantification and future cost-effectiveness. On the other hand, renewed interest in cyclotron-produced ^{99m}Tc may alleviate diminishing supply. Only future will tell!