Challenges in Multi-Center Quantitative Imaging for Radiopharmceutical Therapy (RPT) Dosimetry

Rapid

Precision Medicine for
Radiopharmaceutical Therapy

Disclosure

Johns Hopkins University Licenses an iterative reconstruction code for SPECT to GE Healthcare. Eric Frey, Yong Du, and Bin He are entitled to a share of royalty received on sales by GE Healthcare of this reconstruction code. Portions of that code were used to generate many of the data used in this presentation.

Eric Frey is a co-founder of and 95% employed by Radiopharmaceutical Imaging and Dosimetry (RAPID), LLC. This company was founded to provide quantitative imaging and dosimetry service to developers of radiopharmaceutical therapy agents.

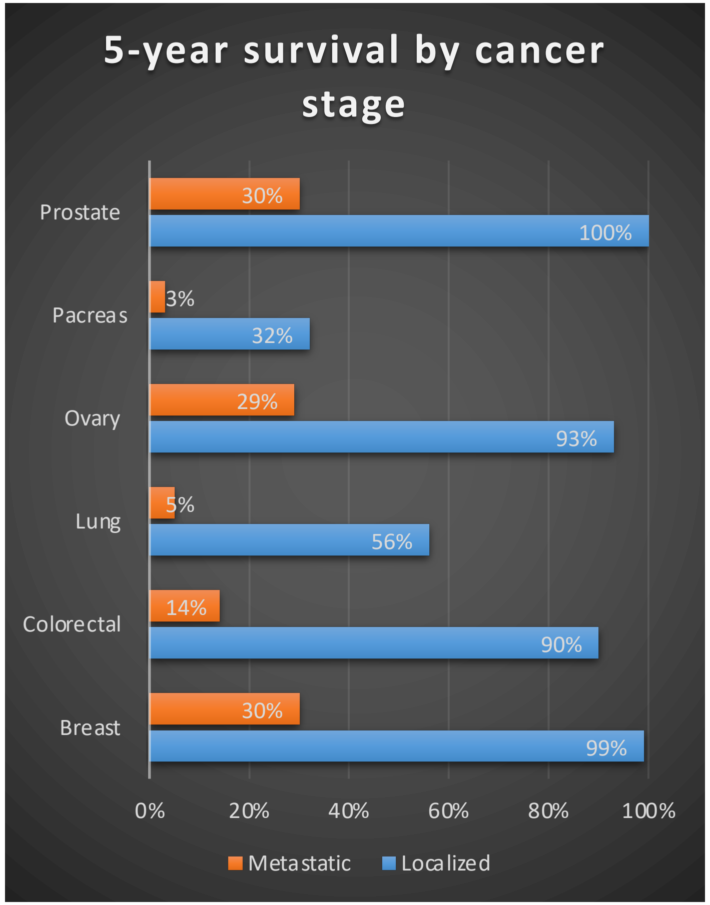
These interests have been disclosed and are being managed by the Johns Hopkins University in accordance with its conflict-of-interest policies.

Outline

- Why RPT for cancer?
- What is RPT dosimetry and how to we do it?
- Radionuclides used in RPT
- How quantitative SPECT works
- Need for calibration in Quantitative SPECT
- Challenges of calibration in multi-center clinical trials of RPT

Why Radiopharmaceutical Therapy (RPT)?

- Survival for patients with metastatic disease is low
- Radiopharmaceutical therapy (RPT)
  - Targets tumor cells
  - Viable treatment option for chemo-refractory and radiotherapy-ineligible patients
  - Radiation kills tumors

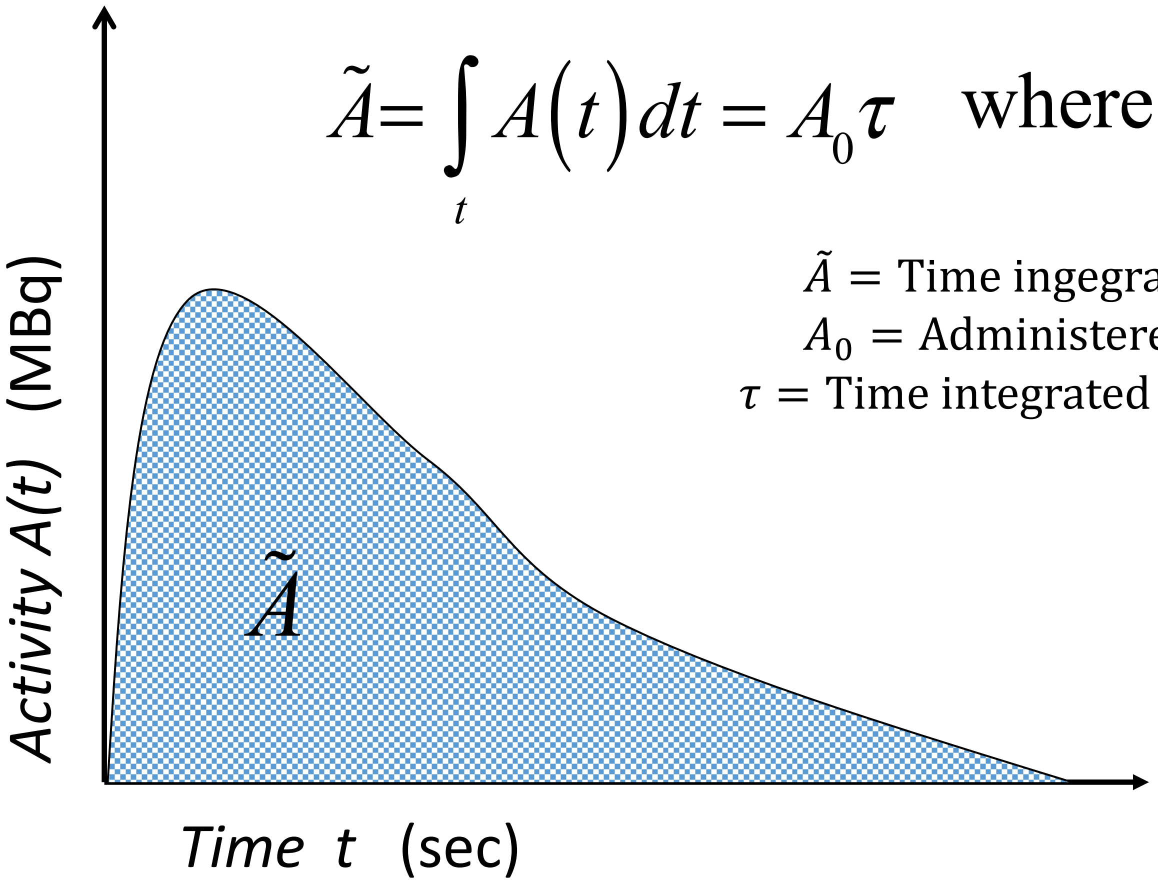


Dosimetry for RPT Treatment Planning

- Need for Dosimetry
  - Biological response related to dose (energy/mass) deposited to tissue
  - Need to estimate dose deposited in tissues
  - Dose related to number of decays=time-integrated activity

Time Integrated Activity and Time Integrated Activity Coefficient

$$\tilde{A} = \int_t A(t)\,dt = A_0 \tau \quad \text{where } \tau = \tilde{A} / A_0$$



$\tilde{A}$ = Time ingegrated activity (TIA) (MBq s)

A_0 = Administered Activity (AA)MBq

τ = Time integrated activity coefficient (TIAC) (s)

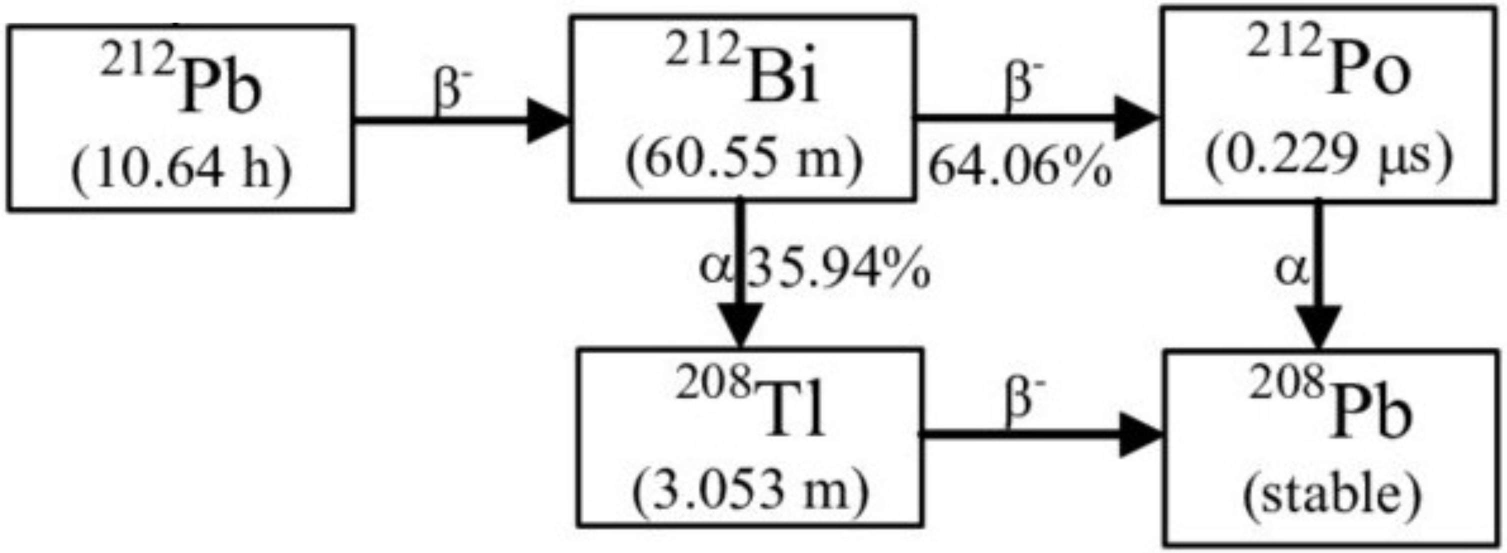
Important Radionuclides in RPT

- Beta emitters
  - I-131
  - Y-90
  - Lu-177
  - Cu-67
- Used in αRPT
  - Ra-223
  - Th-227->Ra-223
  - Pb-212->Bi-212
  - Ac-225
- …

Challenges with Quantitative Imaging of RPT Agents

- Multiple gamma and x-ray emissions
- Presence of high energy photons
- For radionuclides used in alpha emitter RPT (αRPT)
  - Complicated decay schemes with multiple daughters
  - Small administered activities

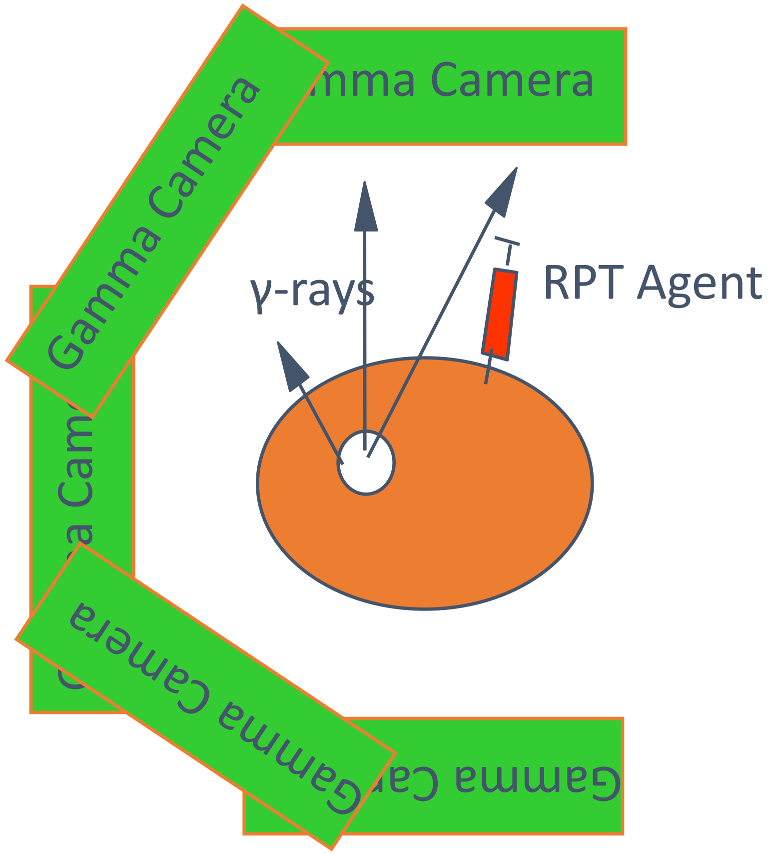
Pb-212



Imageable Photons
E ≥ 50 keV
Abundance ≥ 10%

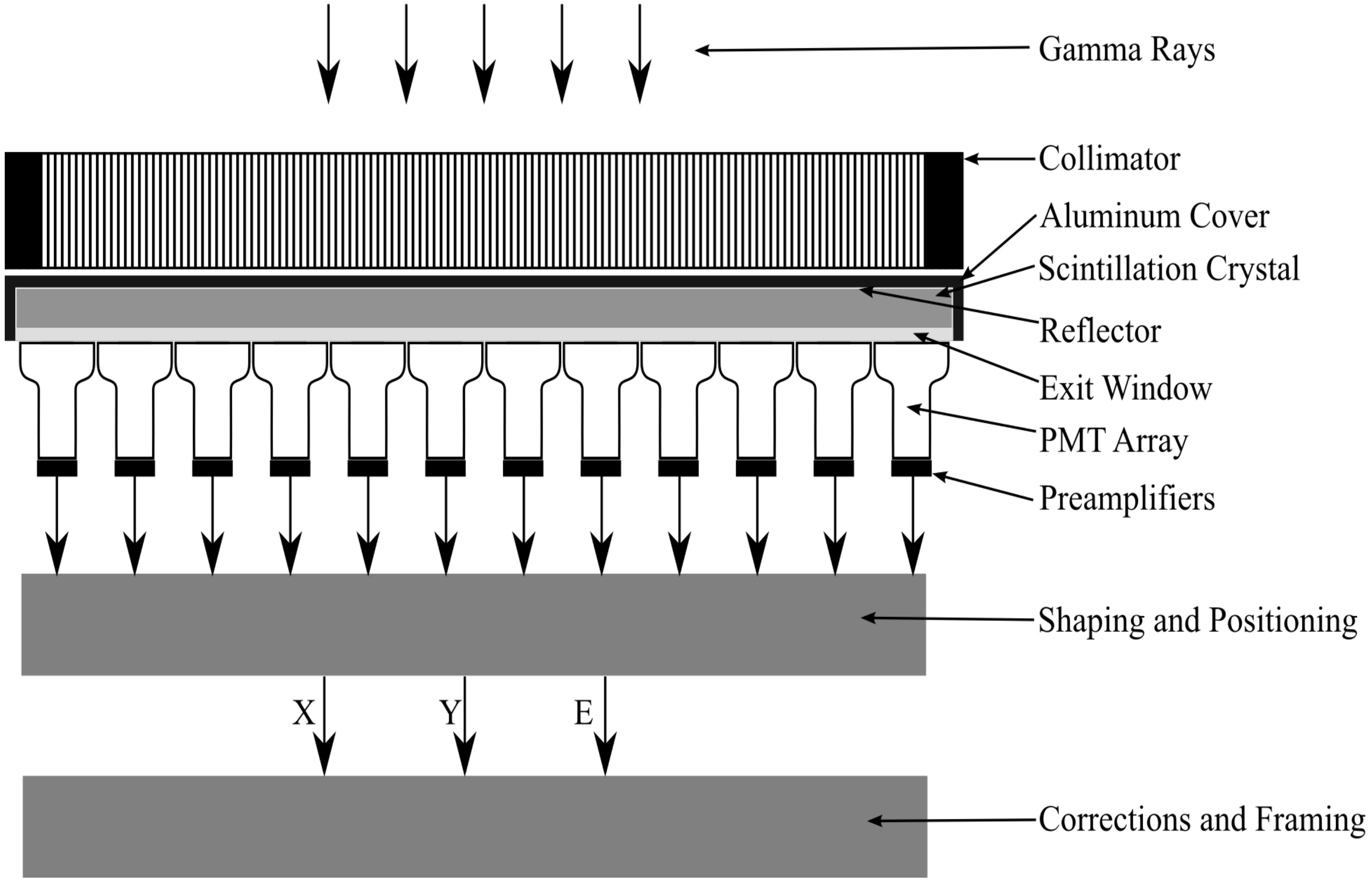
Energy (keV)	Abundance (%)	RN
75.1	10.6	Pb-212
77.4	17.7	Pb-212
238.6	43.3	Pb-212
583.2	30.4	Tl-208
2614.5	35.6	Tl-208

Single-Photon Emission Computed Tomography (SPECT)

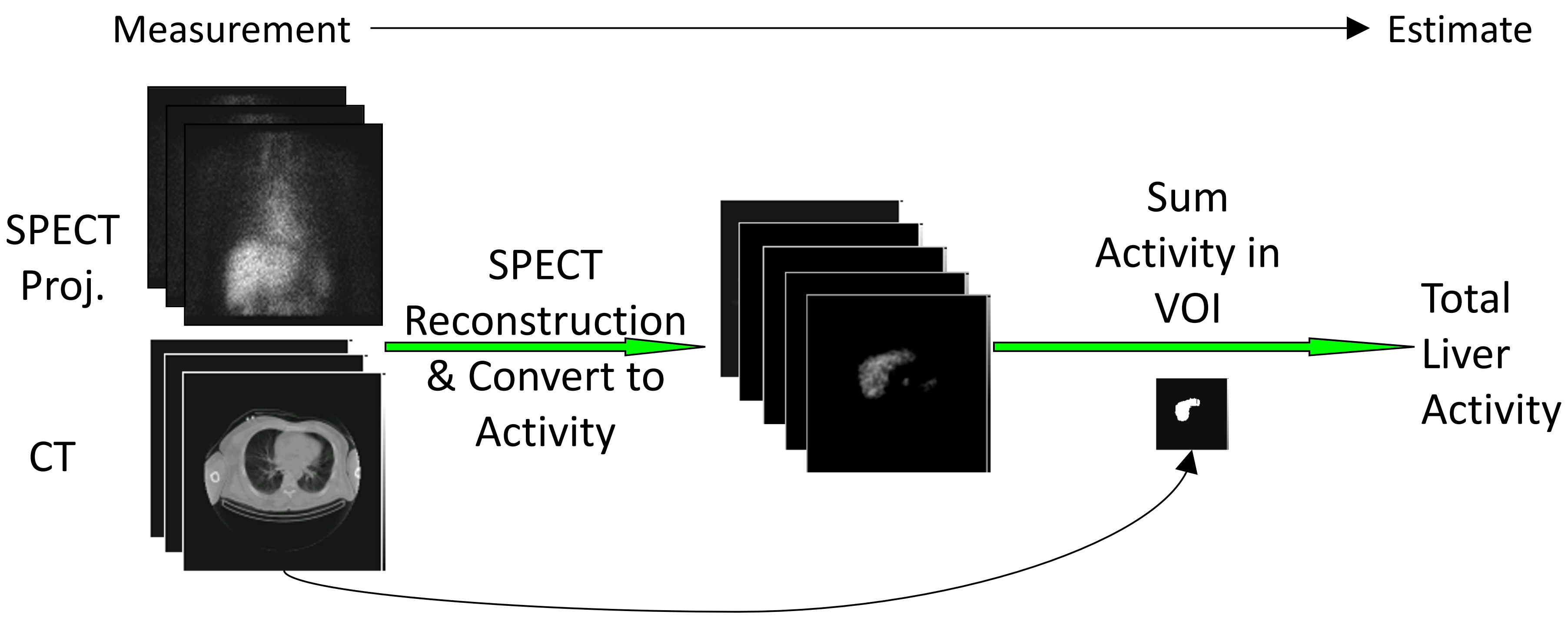


(Scintillation) Gamma Camera

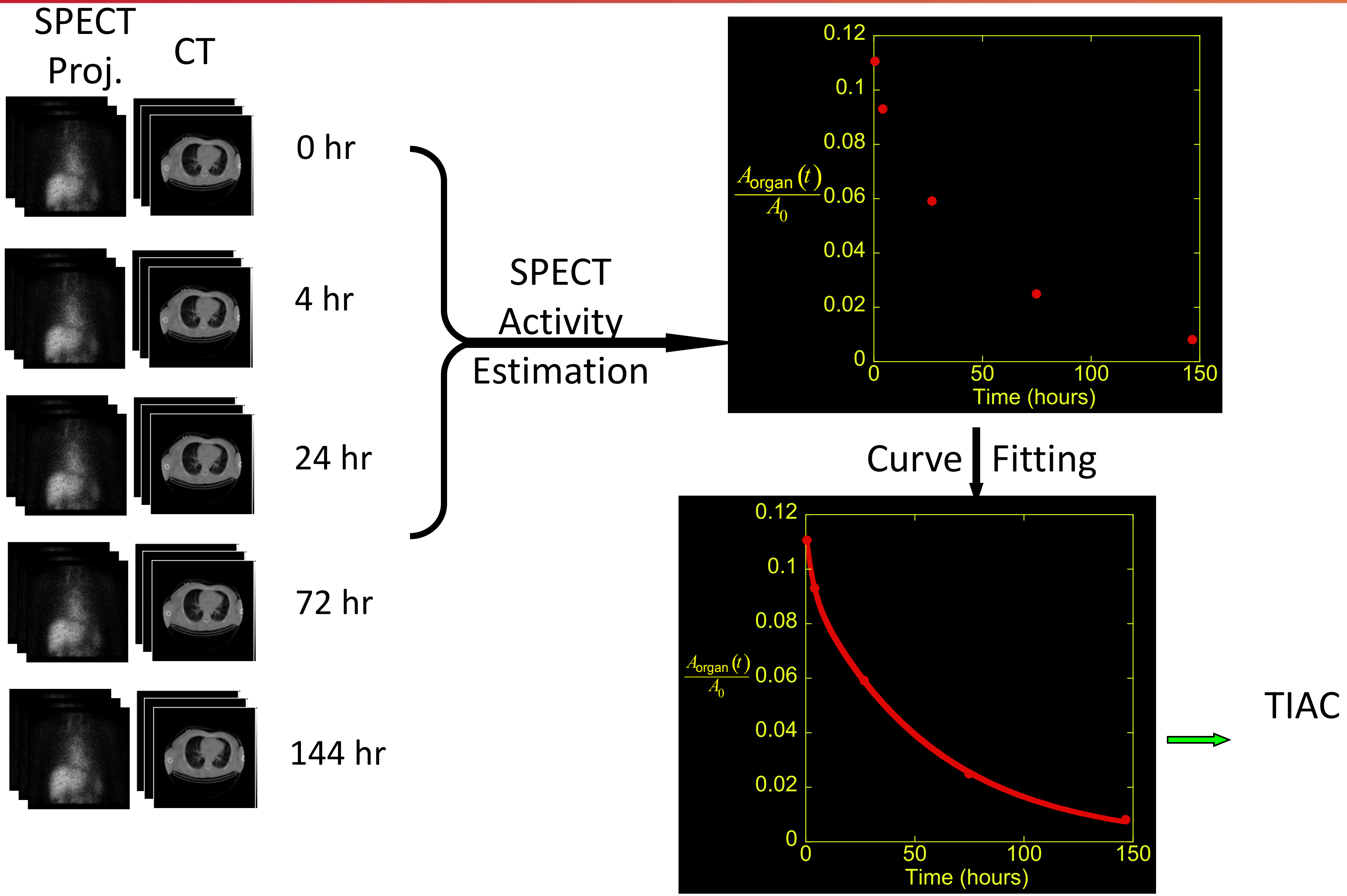
- Overview
  - Typical size: 40x50-60 cm in modern cameras
  - Resolution largely determined by collimator
  - Crystal
    - Optimized for diagnostic imaging (140 keV photons)
    - NaI(Tl)
    - 9.5 cm thick



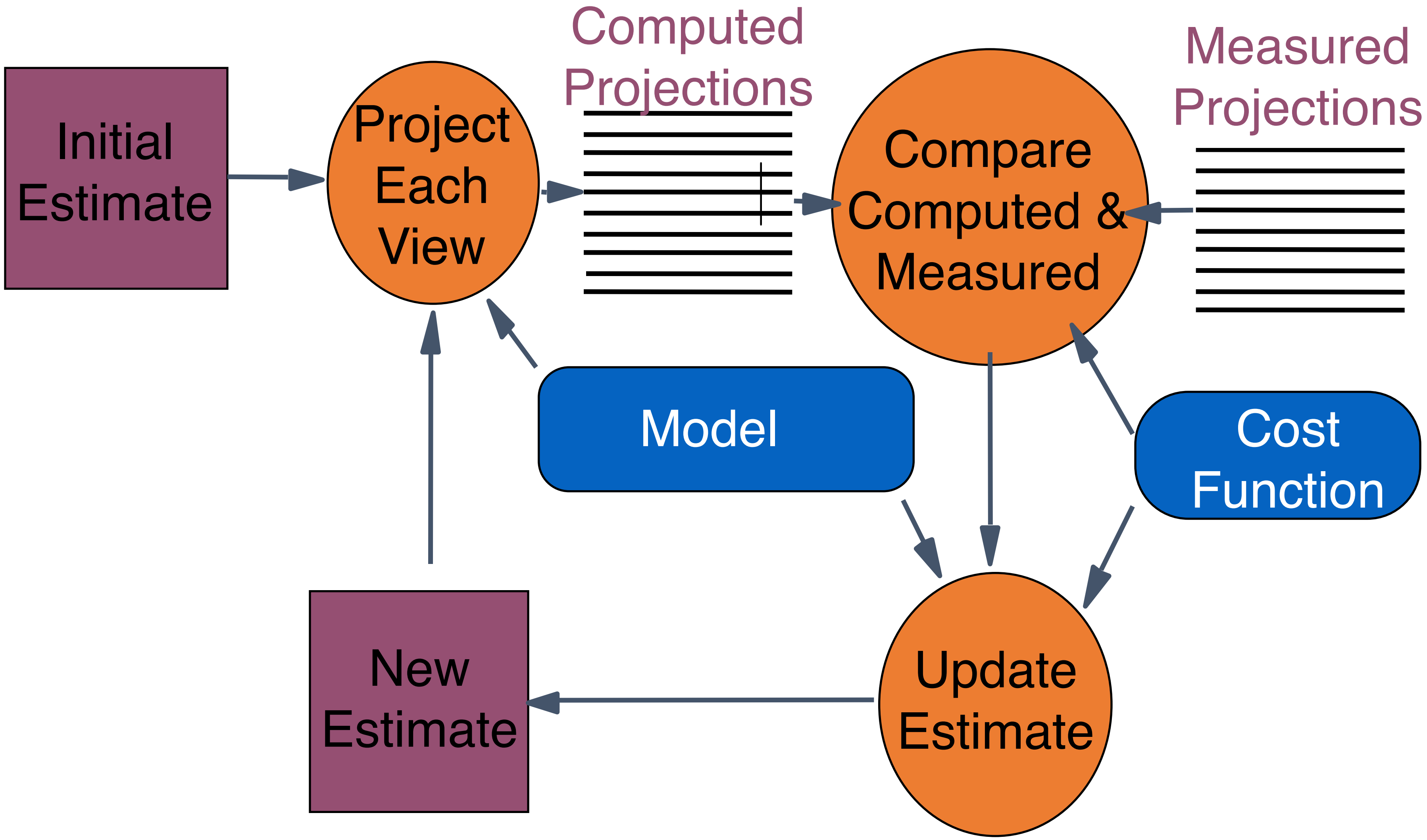
SPECT/CT Organ Activity Estimation



SPECT TIAC Estimation



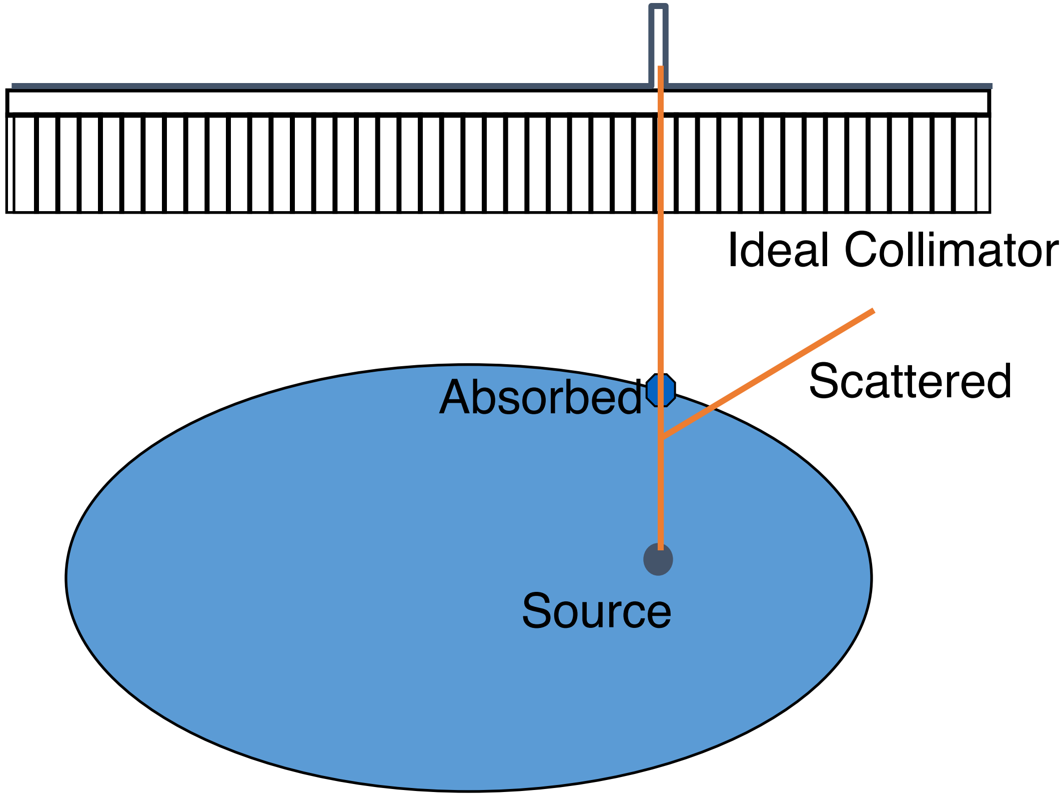
Iterative Reconstruction for Quantitative SPECT



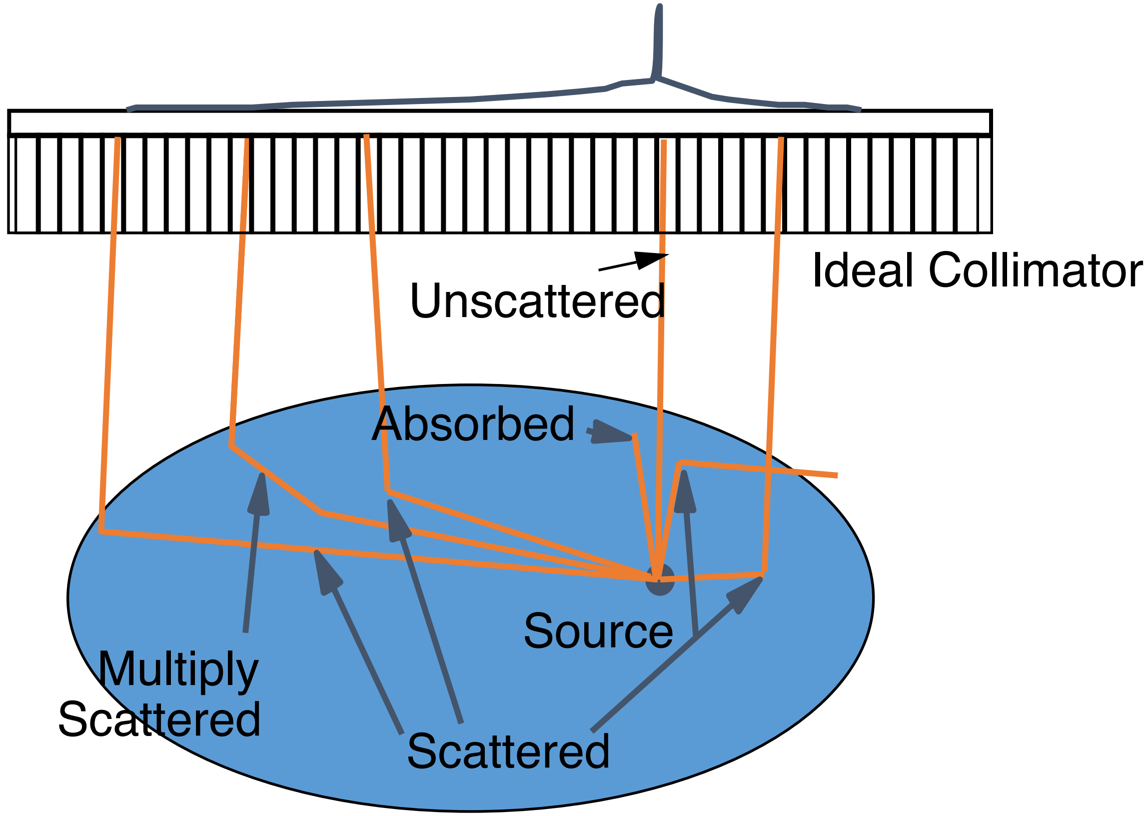
Modeling Image Formation Process

- Attenuation
- Scatter
- Collimator-Detector Response (CDR)
    - Geometric response
    - Septal penetration and scatter responses

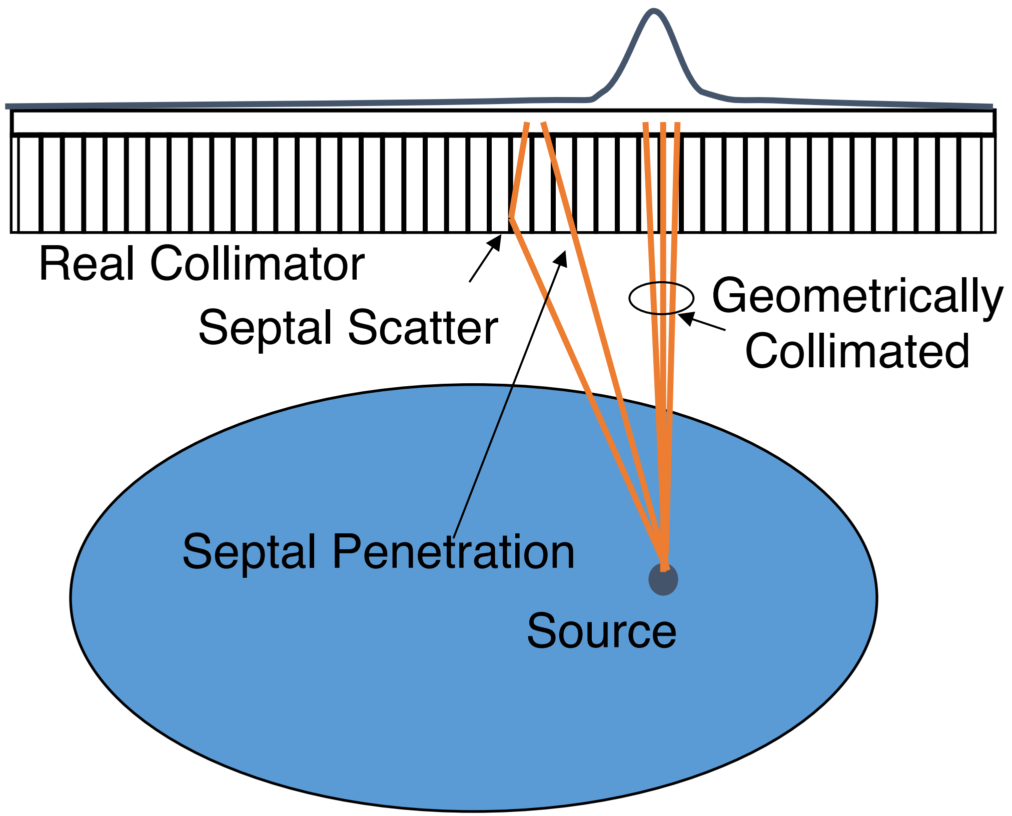
Attenuation in Patient



Object Scatter



Collimator-Detector Response (CDR)

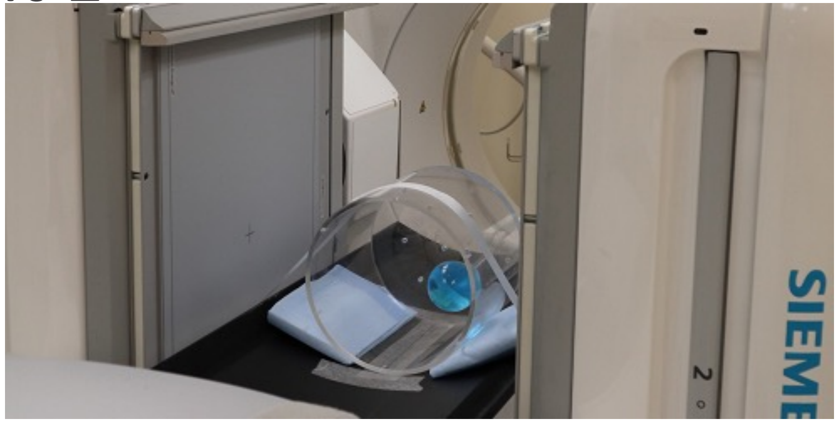


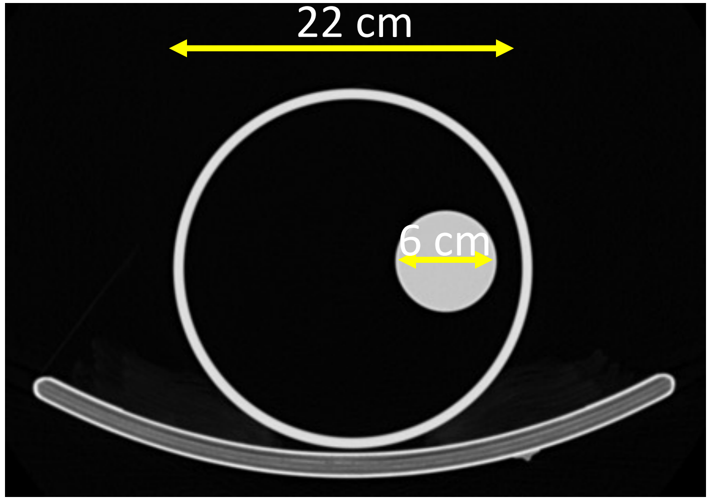
Methods – Validation of MC Simulation for Pb-212

Goal: To evaluate the simulation accuracy when using the acquisition parameters identified in experiment 1

A. Phantom Experiment:

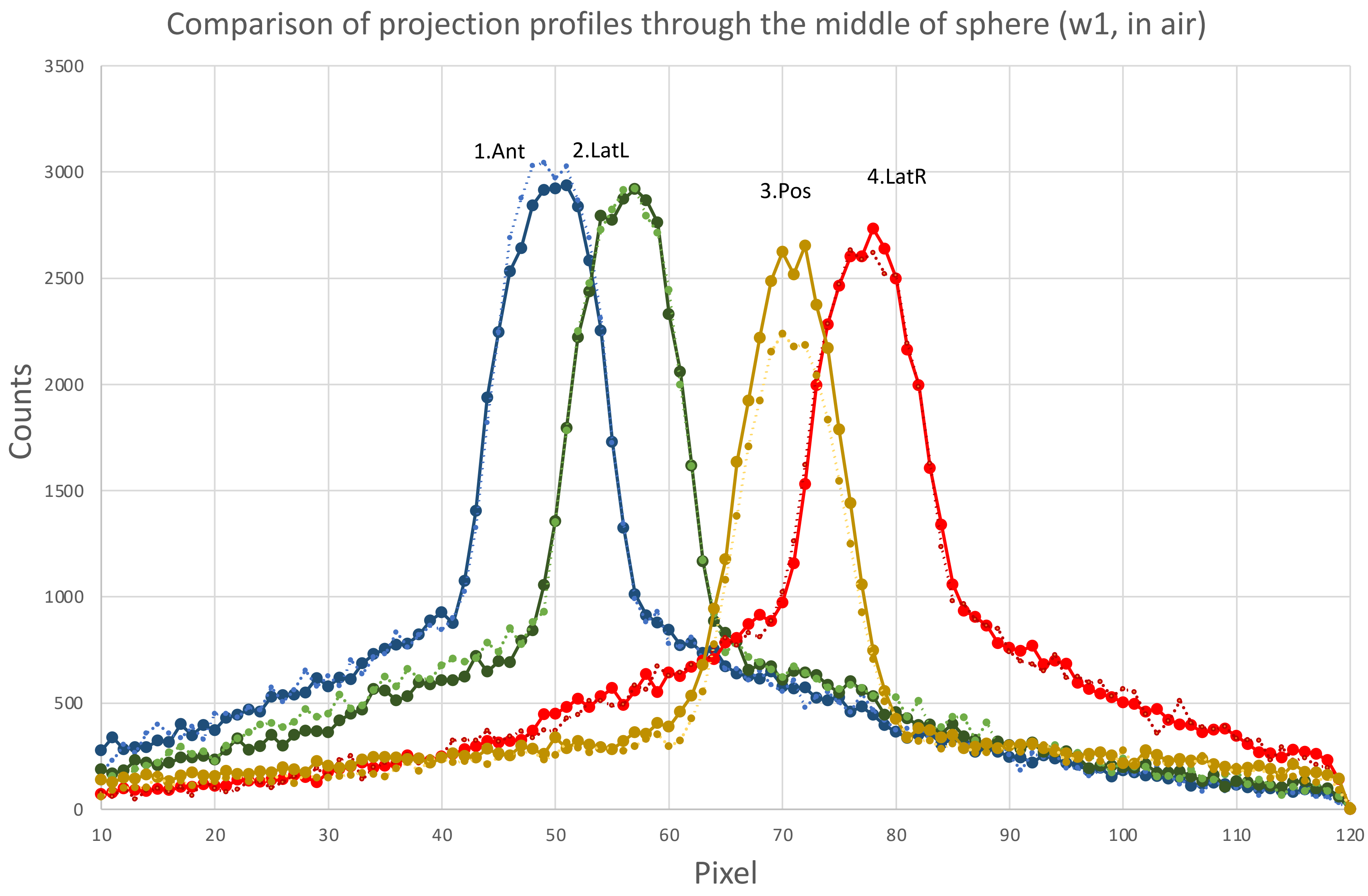
- 6 cm diameter sphere
- 19.39Mbq Pb-212 in sphere
- 22 cm diameter cylindrical phantom
- Phantom filled with
    - Air
    - Water (no activity)



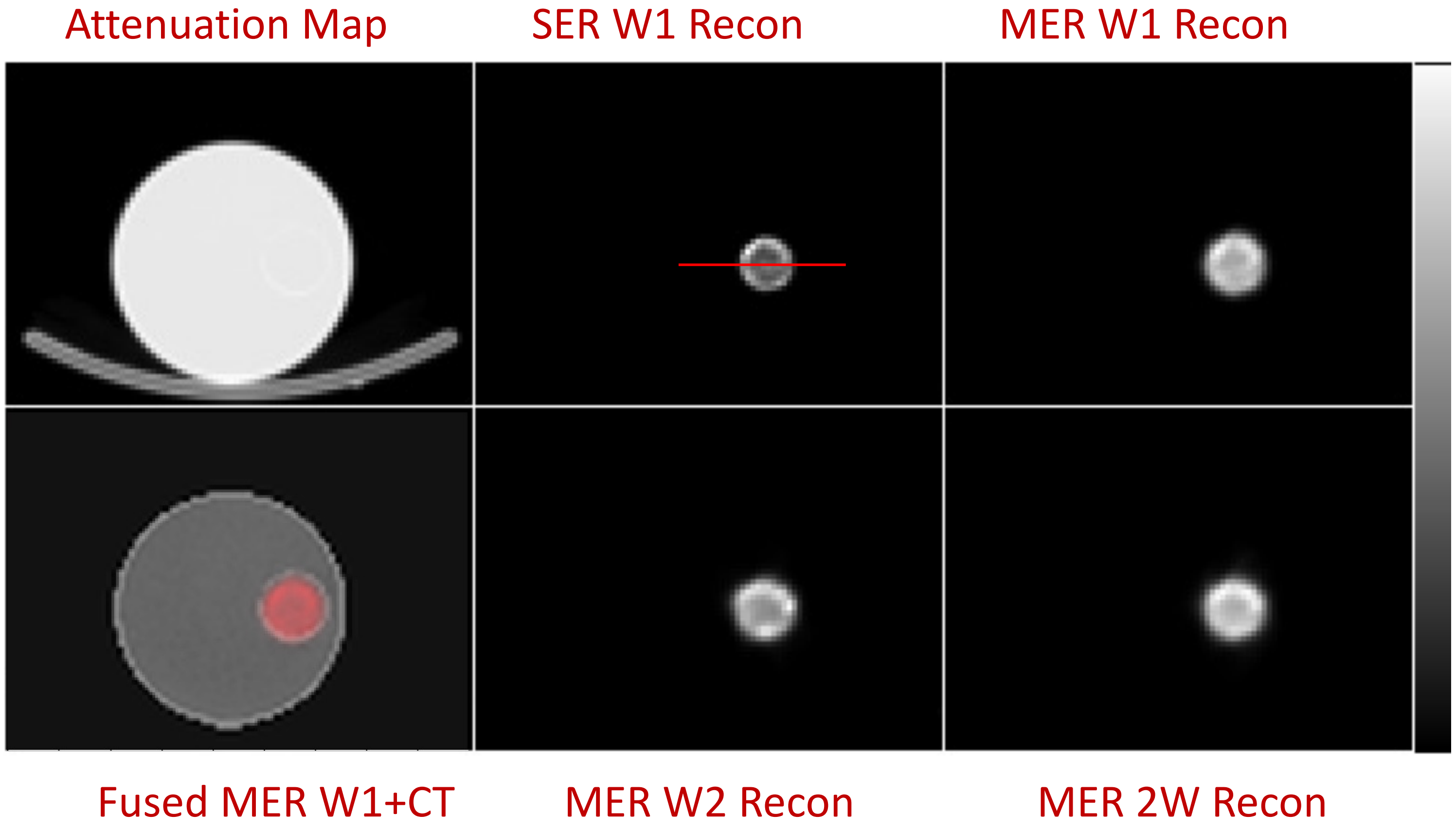


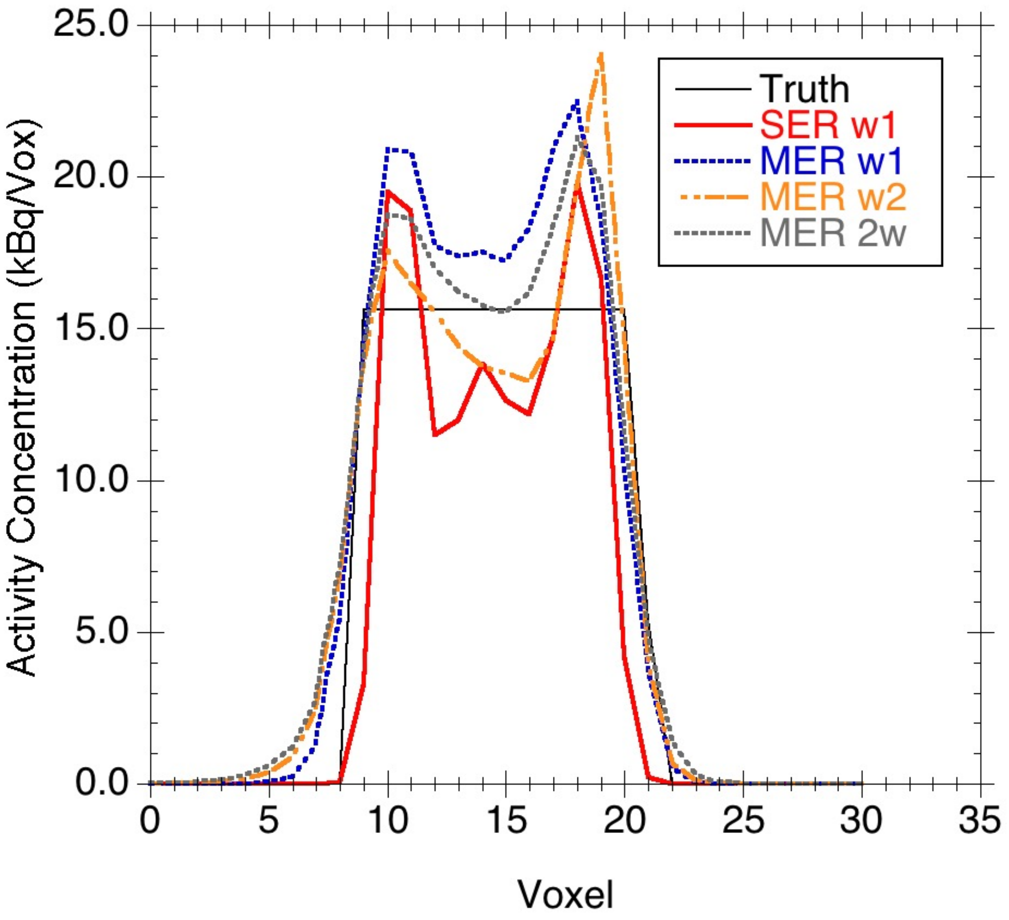
B. SIMIND simulations:
Simulate the same parameters as in physical phantom experiments

Results –Pb-212 Sphere in Air, 67-91 keV Window



Results – QSPECT Reconstructions





Pb-212 Results – Quantitative Accuracy

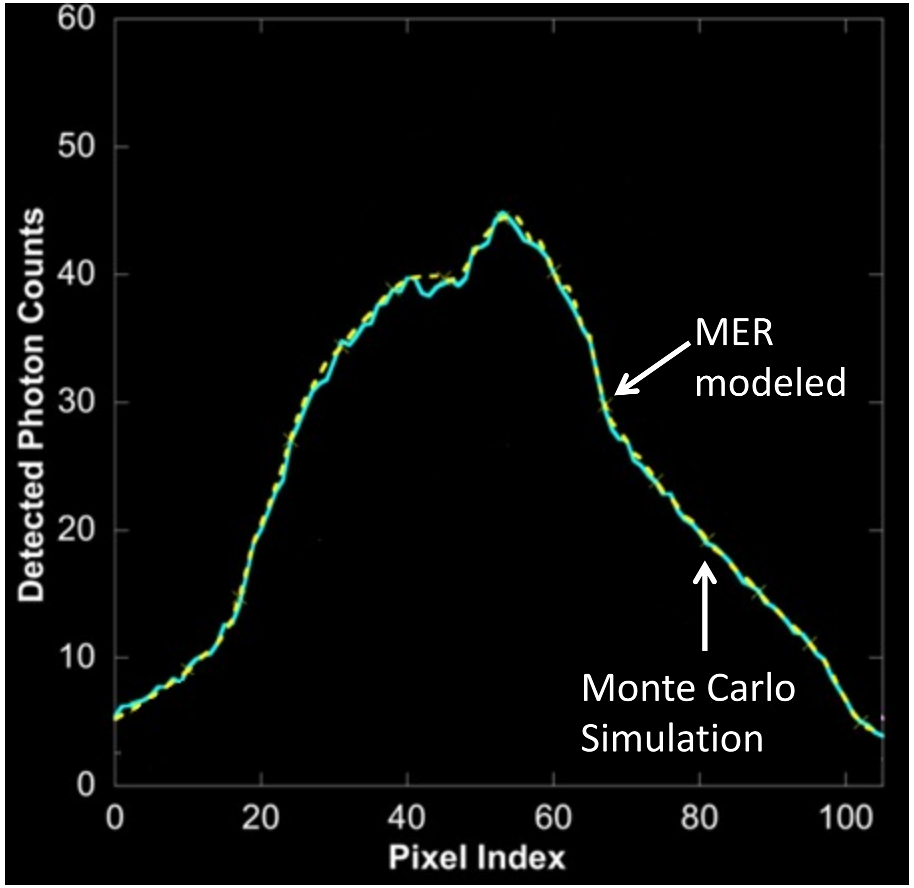
- Sphere activity estimate % errors are calculated by

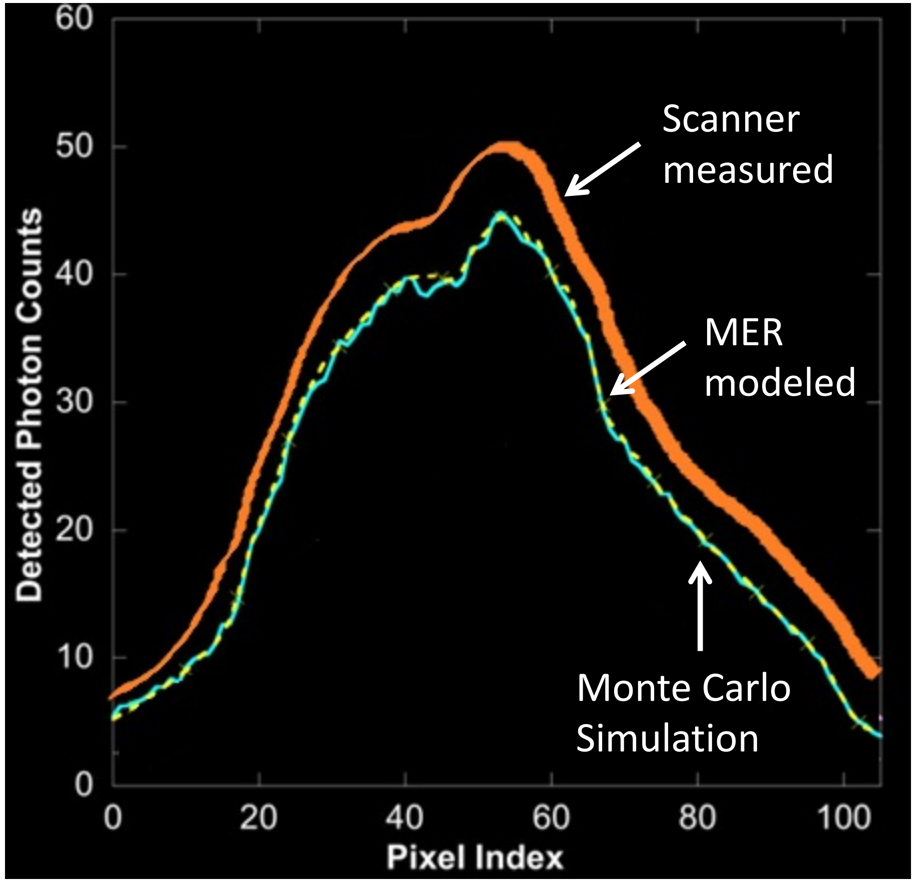
  (estimate activity - true activity) / true activity * 100%.

Negative values indicate underestimation compared to the truth

Recon Method	Sphere Activity Estimate % Error
MER recon from window 1 projection	1.2%
MER recon from window 2 projection	-10%
MER recon from both projections	-4.2%

Need for Calibration: Y-90



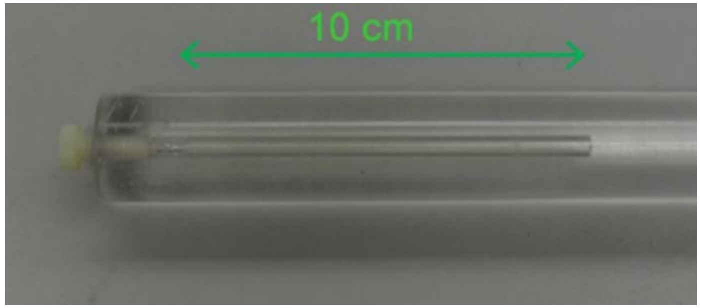


Calibration Methods

- Planar calibration
  - Image of small (cylindrical source)
  - Compare MC simulated and measured counts to obtain calibration factor
  - Easy to prepare and measure
  - Does not take into account
  - Works well for ‘simple’ radionuclides
- SPECT calibration
  - Simple phantom (sphere inside cylinder)
  - Acquire SPECT acquisition
  - Apply QSPECT reconstruction
  - Comparison of activity estimate in image with true activity gives calibration factor
  - Needed for ‘complicated’ radionuclides

Limitations of Planar Calibration
Quantitative Y-90 SPECT

Planar Calibration



Scanner	Calibration Factor
GE Discovery 670	1.14
Siemens Symbia	1.08

SPECT Calibration

Phantom	Dimensions
Large Uniform Cylinder	20 cm diameter
Small Uniform Cylinder	4.6 cm diameter
Sphere in cold Elliptical Phantom	5.5 cm diameter sphere in 32x20 phantom

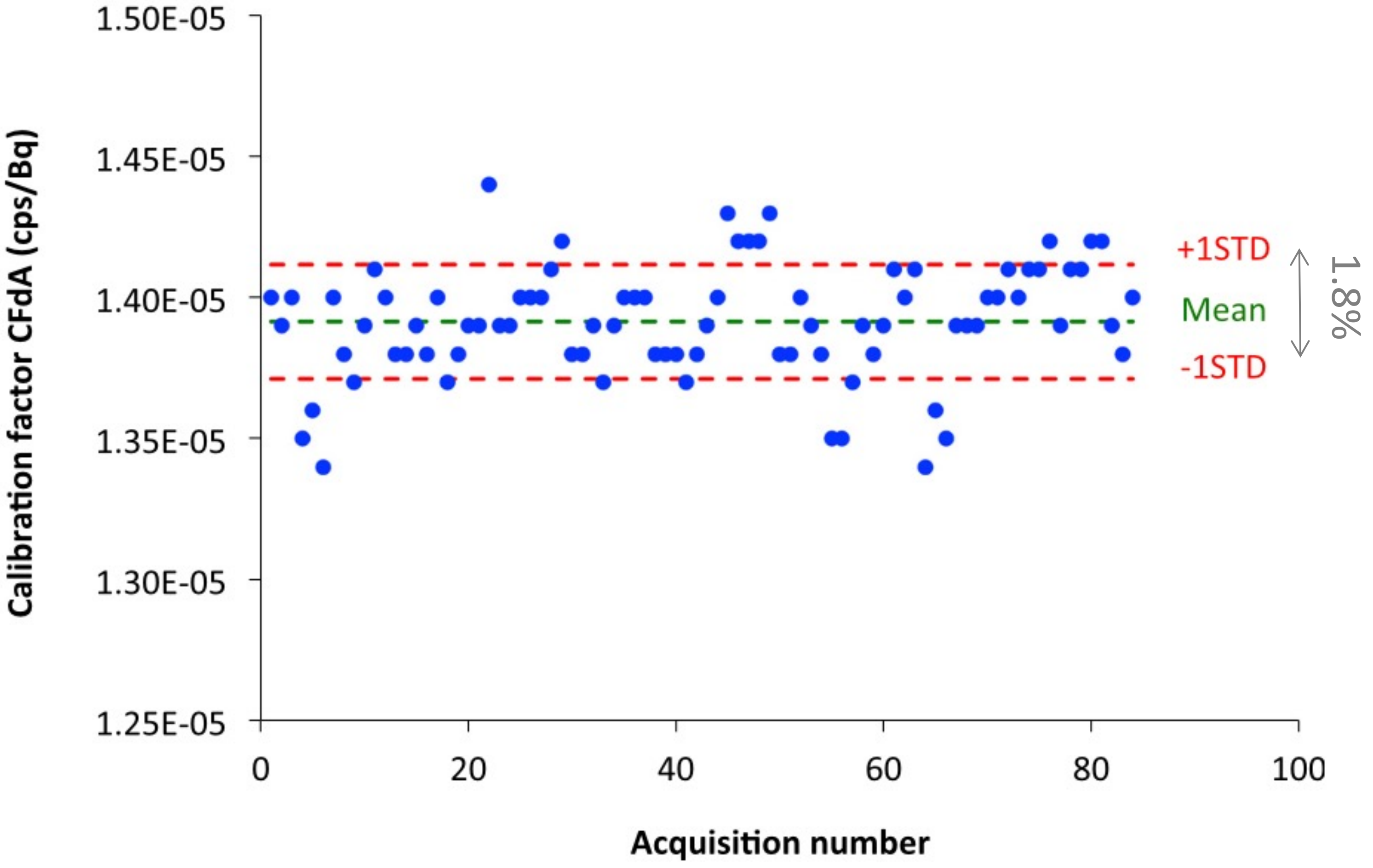
Scanner	Calibration Factor
GE Discovery 670	1.21-1.23
Siemens Symbia	1.15-1.18

Variations in Calibration Factor over Time: Single Camera

- Retrospective review of calibration factor from I-131 Bexxar therapies
- Wholebody scan of vial with known I-131 activity on 3 days
- 46 patients
- Time period: 2007-2011

Anizan N, Wang H, Zhou X, Hobbs R, Wahl R, Frey E. Factors affecting the stability and repeatability of gamma camera calibration for quantitative imaging applications based on a retrospective review of clinical data. EJNMMI Research. 2014;4(1):67.

Variations in Calibration Factor



- Largest source of variation (77% of variance) was due to inter-source effects
- Suggests that consistent preparation and measurement of source activity is key

Variation in Lu-177 Calibration Factors: Multiple Cameras

- 15 sites
- Siemens Symbia
- Same energy window
- Variation in phantoms
- Activity calibration unknown
- 2 outliers
- Overall variation was large (~10%)
- Some of variation due to differences in phantoms used at sites

Site	CF
1	0.8155127
2*	0.62533147
3	0.83897265
4	0.82203979
4	0.81478291
5*	0.63389292
6	0.82795
7	0.76982
8	0.91724
9	0.91701
10	0.86402
11	0.89804
12	0.79862
13	0.82021
14	0.75293
15	0.74062

Mean CF	COV (%)
0.80660403	9.7%

*Outliers ignored

Variation in Ra-223 Calibration Factor: Multiple Cameras

- Ra-223
- Images of sphere in cylindrical phantom
  - Not all phantoms are the same
  - 2 different scanner manufacturers
  - 3 different scanner models
  - 4 different sites
  - 3 energy windows

Variation in Ra-223 Calibration Factor: Multiple Cameras

	Camera	71-97 keV	138-169 keV	248-289 keV
Site 1	Siemens Symbia 1	1.17110	1.23042	1.13903
Site 1	Siemens Intevo 1	-	1.25128	1.17986
Site 2	Siemens Symbia 2	0.92352	0.96284	0.85793
Site 3	Siemens Symbia 3	0.87192	0.87887	0.81109
Site 3	Siemens Symbia 4	0.90114	0.95490	0.93097
Site 1	GE Discovery 670	1.29937	1.35468	1.11357
Site 4	GE Discovery 670	0.85568	1.00023	1.09538
Site 5	GE Discovery 670	0.79080	0.99143	0.96344

Variation over vendor (expected due to different collimator designs)

Variation over energy window (errors in energy calibration?, differences in actual and modeled camera parameters?, accuracy of reconstruction)

Variation over site (differences in activity measurement?, phantom?, filling technique?, actual camera parameters?)

Need: Gamma camera calibration techniques

Scientific or Technical Challenge

- Calibration of gamma camera systems used in imaging radionuclides used in radiopharmaceutical therapy is urgently needed
- Accurate measurement of activity, filling phantoms, and imaging of phantoms is needed at multiple clinical sites with different scanners

Potential Scientific or Technological Impact

Reduced variability of patient dosimetry resulting in less uncertainty in organ MTD and tumor therapeutic dose

Summary of research direction

- Many radionuclides: Lu-177, Y-90, I-131, Cu-67, Pb-212, Ra-223, Th-227, Ac-225,…
- Develop sealed source methods and procedures for calibrating cameras for a variety of radionuclides
- Radionuclides for the source must be selected
- Methods for cross-radionuclide calibration are needed

Acknowledgements

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