An Overview of ***Activity*** within the NIST Laboratory for Quantitative PET/CT Imaging

Matthew M. Mille

22nd Annual CIRMS Meeting
3/12/14

National Institute of
Standards and Technology
U.S. Department of Commerce

Acknowledgements

- Team effort within NIST radioactivity group
  - Brian Zimmerman, Denis Bergeron, Jeff Cessna, Heather Chen-Mayer *et al.*
- Collaborations with Rensselaer Polytechnic Institute, University of Iowa, Radqual LLC
- Fellowship Support
  - DOE Nuclear Energy University Fellowship (2010-2013)
  - Burton J. Moyer Fellowship (2009-2010) sponsored jointly by Health Physics Society (HPS) and Northern California Chapter of HPS

Outline

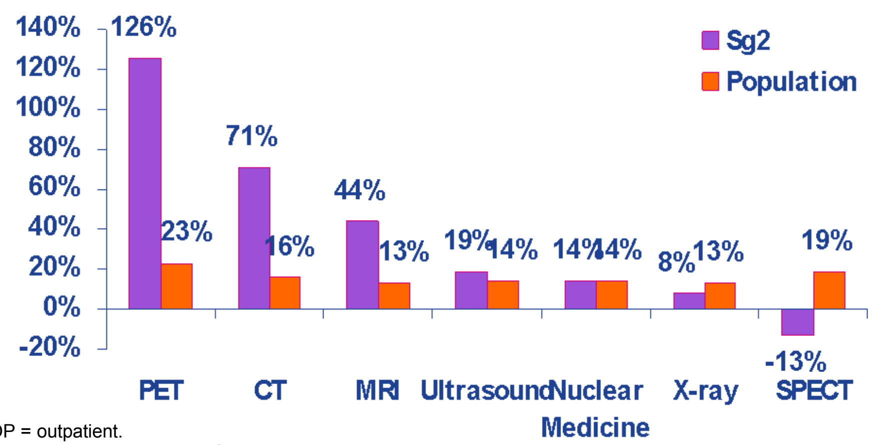
- Introduce Quantitative PET/CT
- Discuss measurement challenges & need for PET standards
- Founding of NIST lab for quantitative PET/CT
- Report on past & on-going activities
- Goals for the future

The Rise of PET/CT
"Two Modalities are Better than One"

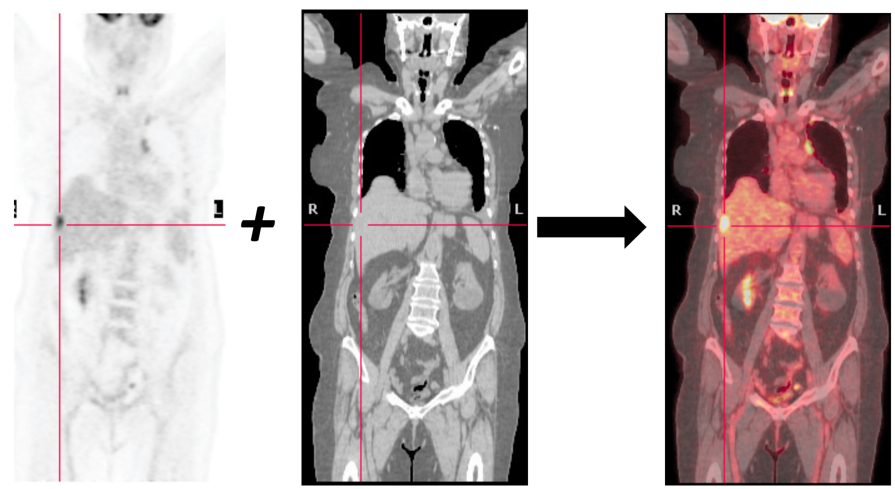
- PET/CT scanners—functional and anatomical imaging in single exam
- Combine strengths of high sensitivity (PET) and precise localization (CT)
- Tremendous impact on cancer management and drug discovery

Large Growth of PET/CT

Percent Change in Outpatient Imaging Volumes
US Market, 2008–2018

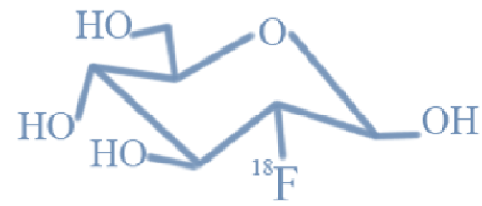


OP = outpatient.
Sources: Impact of Change® v7.0; Pharmetrics; HCUP; CMS; CDC; Sg2 Analysis, 2008.

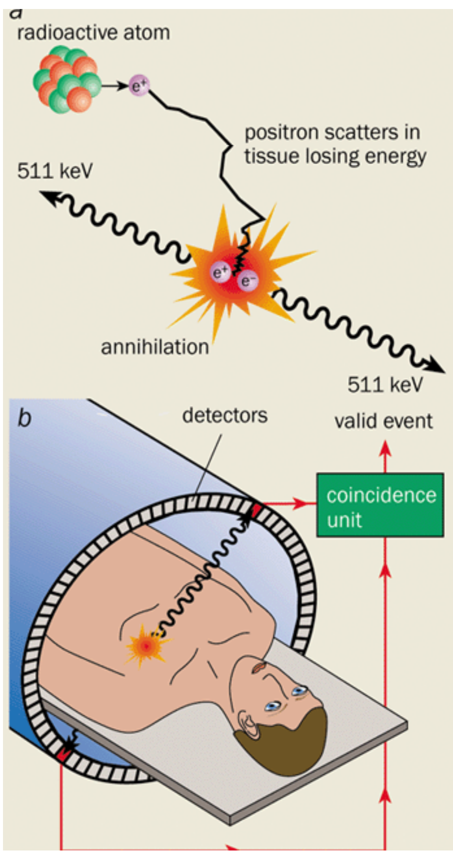


PET **CT** **Fused PET-CT**

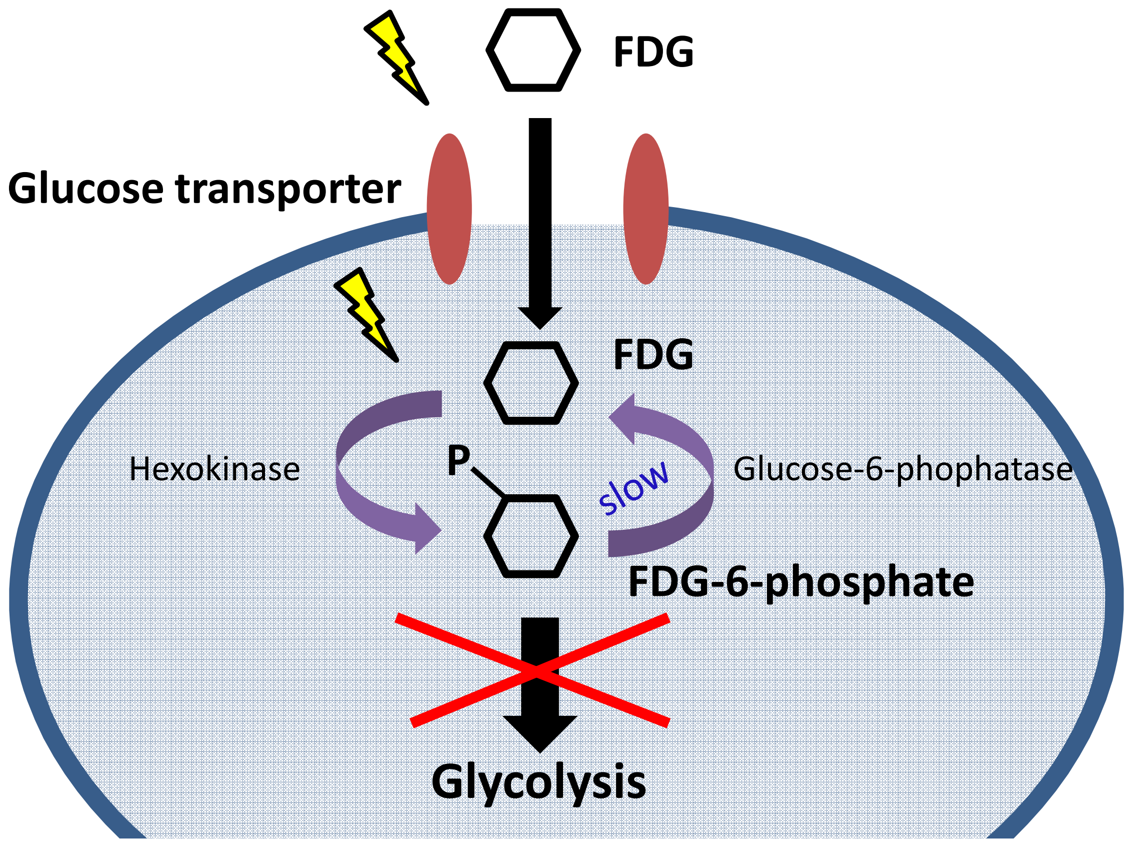
Physics and Biology of F-18 FDG



- **F-18 radioisotope**
  - Produced in cyclotron
  - Decays via positron emission (96.73%) to stable ^{18}O
  - Positron annihilation
  - Half-life 109.77 min

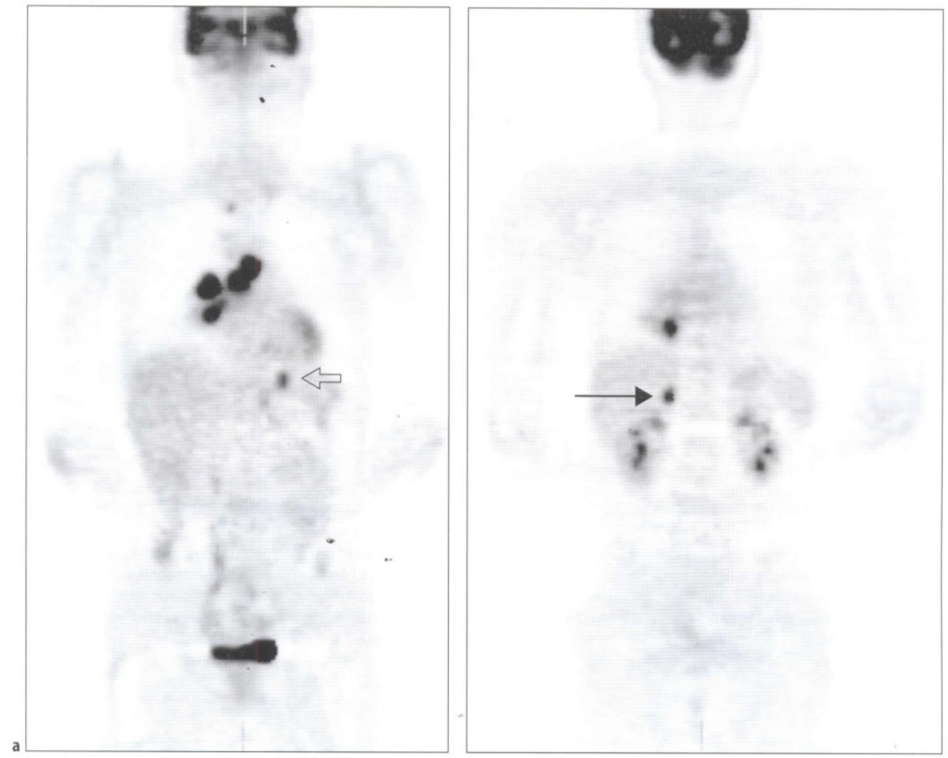


- **Fluorodeoxyglucose**
  - Hypermetabolic cells need glucose to replicate
  - Acts like glucose except:
    1) Transported into cells but not metabolized (i.e. becomes trapped)
    2) Excreted in proximal tubules of kidneys (i.e. low body background, high SNR)



Advantages of FDG PET in Oncology

- Distinguish malignant vs. normal biology
- Detect cancer earlier than with CT or MRI
- Monitor response of tumor to therapy
- **Quantitative Imaging!**



F-18 FDG

Biomarker cellular metabolism

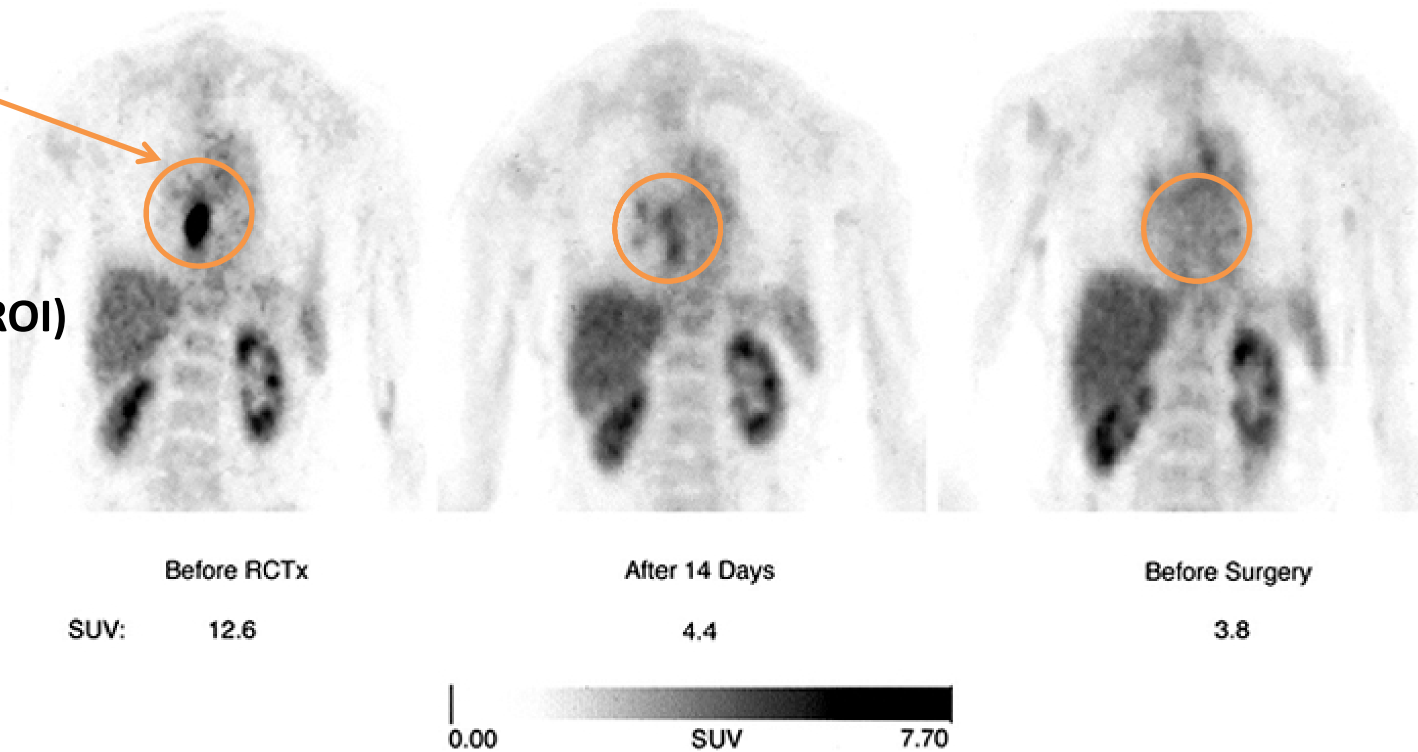
Quantify

PET Image ~ 3D Radioactivity Distribution ~ Drug Uptake ~ Clinical Interpretation

PET Can Be Quantitative

Voxel intensity is proportional to activity concentration

Mean or maximum SUV over region of interest (ROI)



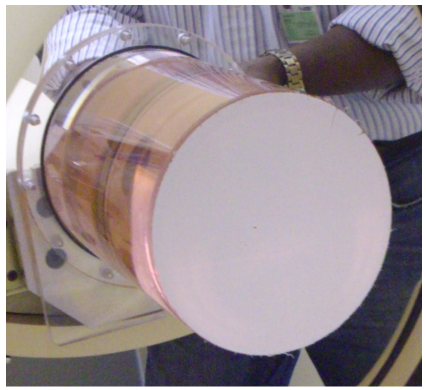
Standardized Uptake Value

$$SUV_{bw} = \frac{Activity\ Concentration\ (Bq/mL)}{\underset{at\ scan\ time}{Injected\ Dose}\ (Bq)/Patient\ Weight\ (g)}$$

Quantitative Technique

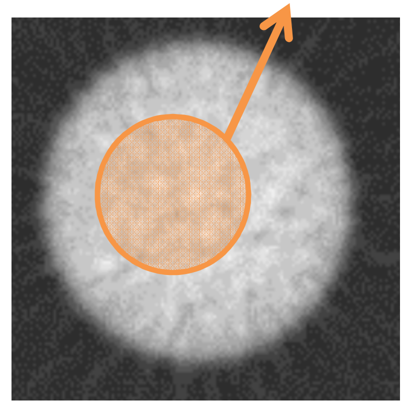
Dose calibrator

Known **A** kBq/mL



phantom

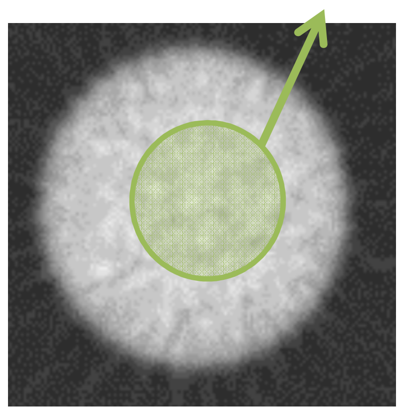
Measured **C** counts/s/voxel



phantom

CF=A/C

Unknown Patient with **P** counts/s/voxel

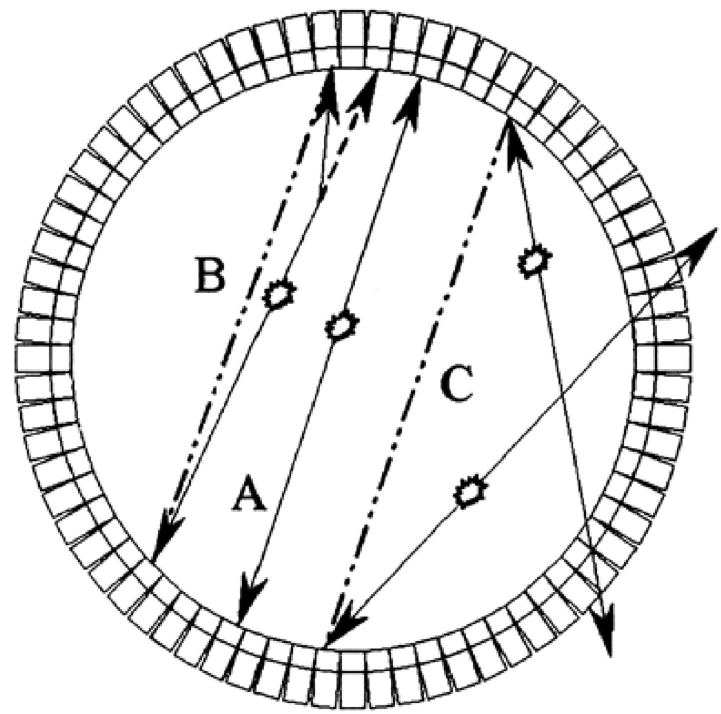


Activity Conc. = CF × P

<u>**However,**</u> without multiple corrections there is no simple relationship between activity and pixel value.

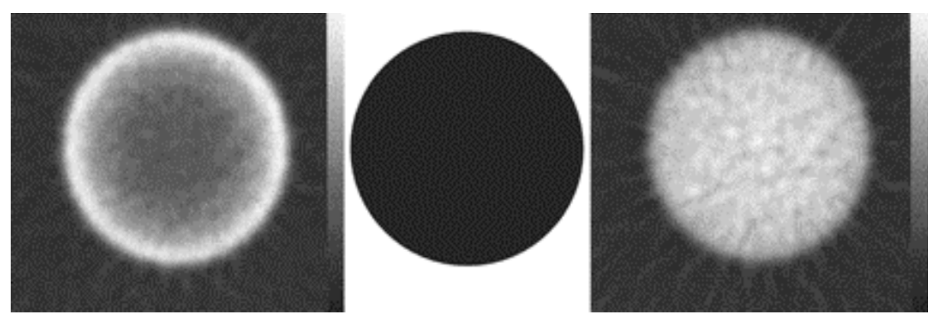
Sources of Quantification Error/Uncertainty

Biological Factors
"uptake time", glucose level, motion, muscle activity, *etc.*



Instrumentation Factors
Spatial resolution, sensitivity, noise, repeatability, calibrations and corrections —random & scatter coincidences, attenuation, decay, deadtime, partial volume effects, *etc.*

Image Analysis Factors
art of drawing ROI, ROI metric (e.g. mean or max), treatment of boundary voxels, digits displayed*, etc.*



Lack of Quantitative PET Standards

- No way to ensure dose calibrator is directly linked to scanner, that calibrations from two clinical sites are related, that their calibration has not changed
- Standards can help reduce variability between scans, scanners, and clinical sites
- Important implications for data sharing in multicenter clinical trials

New Lab At NIST for Quantitative PET Imaging

Mission

"To develop standards and PET/CT measurement techniques and act as a reference for interlaboratory phantom comparison"

No patients, just <u>physics and phantoms</u>

Philips Gemini TruFlight* PET w/ 16 slice CT

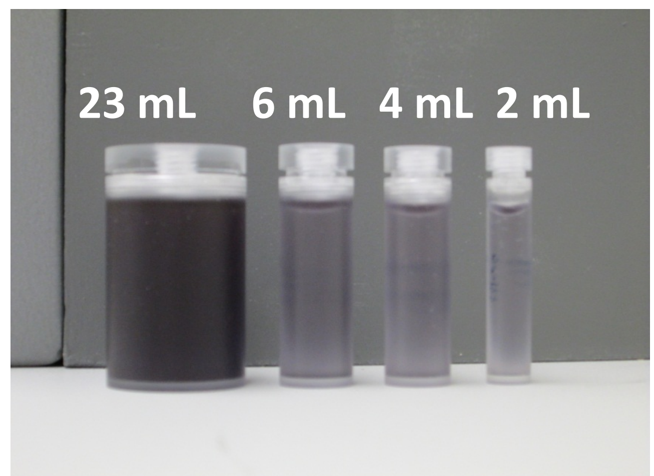
- 28,336 LYSO Crystals
- 44 Crystal Rings of diameter 90 cm
- Coincidence Timing window, 6 ns
- Time of Flight, 575 ps (~8.6 cm)

**Certain commercial equipment, instruments, or materials are identified in this paper to foster understanding. Such identification does not imply recommendation by the National Institute of Standards and Technology, not does it imply that the materials or equipment identified are necessarily the best available for the purpose.*

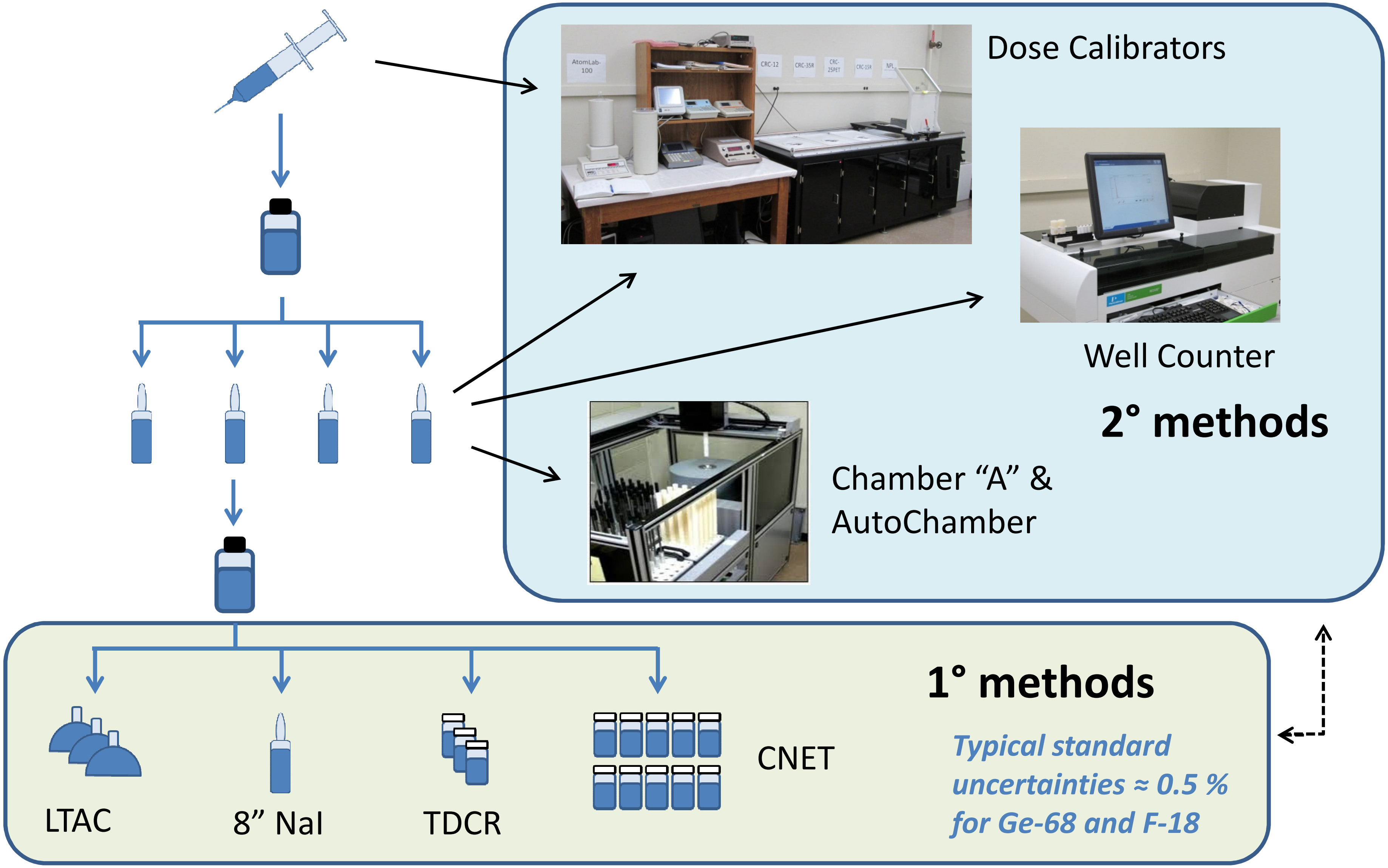
Nuclear Medicine Standards At NIST

NIST is pursuing a program to bring rigorous traceability to activity measurements in nuclear medicine.

- Primary activity standards in 5 mL ampoules
- Dose calibrator dial settings, geometry effects, and calibration protocols
- Traceable phantom inserts
  - Prepared gravimetrically to establish a direct link with primary standards
  - Diameters range from 10 to 30 mm



NIST Primary and Secondary Standards



NIST Dose Calibrators

NIST maintains 7 reentrant ionization chambers (dose calibrators)

- 5 Capintec models, 1 Biodex, 1 Vinten/Keithley*

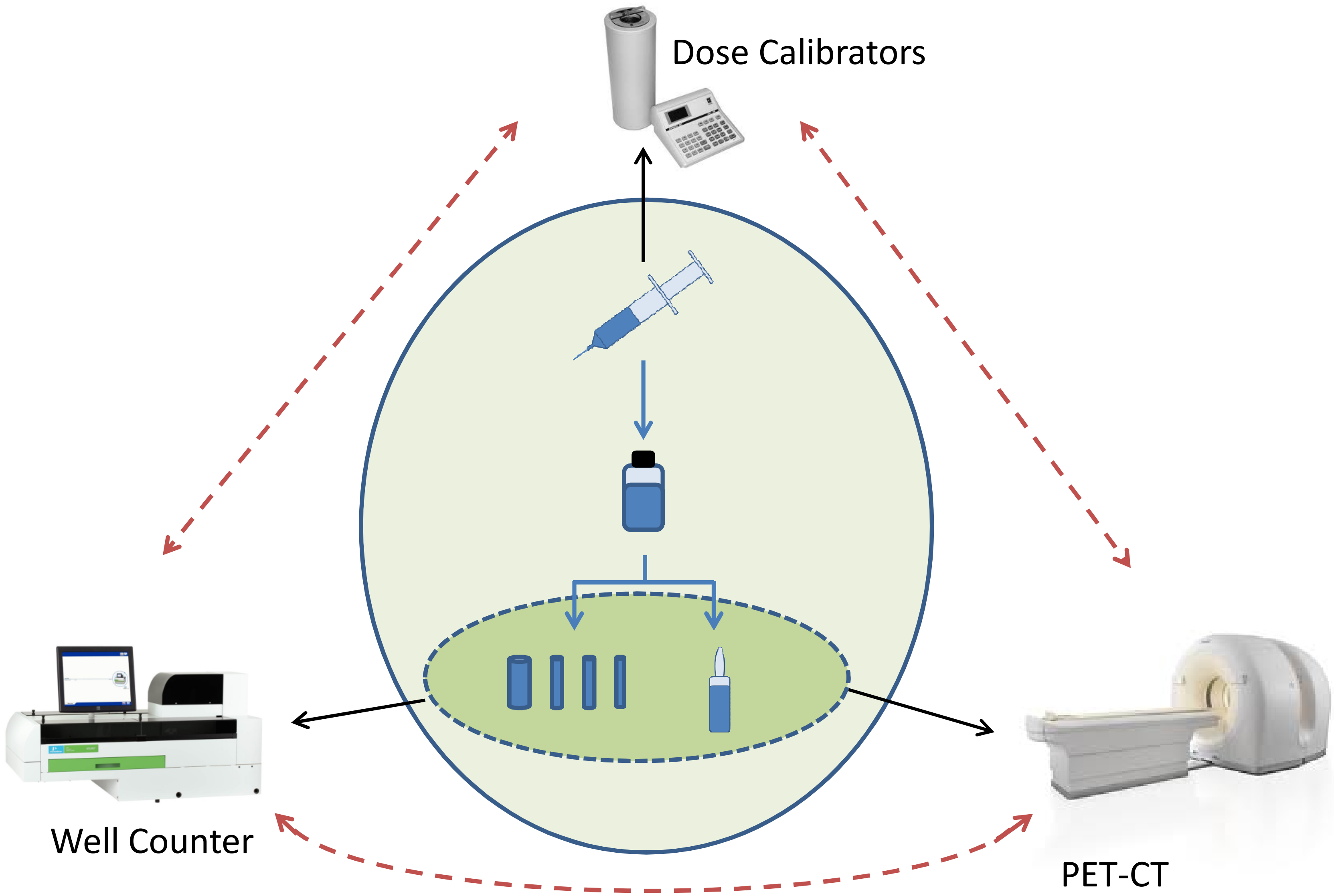
Certain commercial equipment, instruments, or materials are identified in this paper to foster understanding. Such identification does not imply recommendation by the National Institute of Standards and Technology, not does it imply that the materials or equipment identified are necessarily the best available for the purpose.

NIST Well Counter

- NIST acquired a Wallac Wizard 2480 automatic NaI(Tl) well counter* in 2011
- Lower level counting
  - Phantom inserts
  - Small animal
- Currently establishing achievable precision & uncertainties

**Certain commercial equipment, instruments, or materials are identified in this paper to foster understanding. Such identification does not imply recommendation by the National Institute of Standards and Technology, not does it imply that the materials or equipment identified are necessarily the best available for the purpose.*

Linked Calibrations & PET Recovery



Development of Surrogate Standards for F-18

109.7 min

NIST

270 days

^{18}F Primary Standard

^{68}Ge Primary Standard

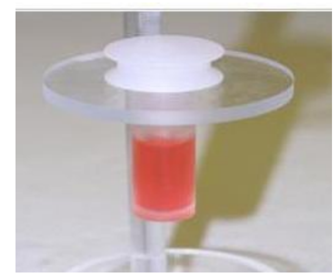
DOSE CALIBRATOR

^{18}F Syringe

Response Factor

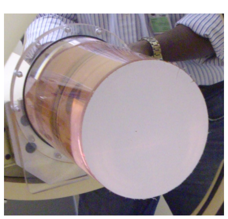
^{68}Ge "Mock" Syringe Standard

Epoxy



PET SCANNER

Liquid



^{18}F Phantom

Correction Factor

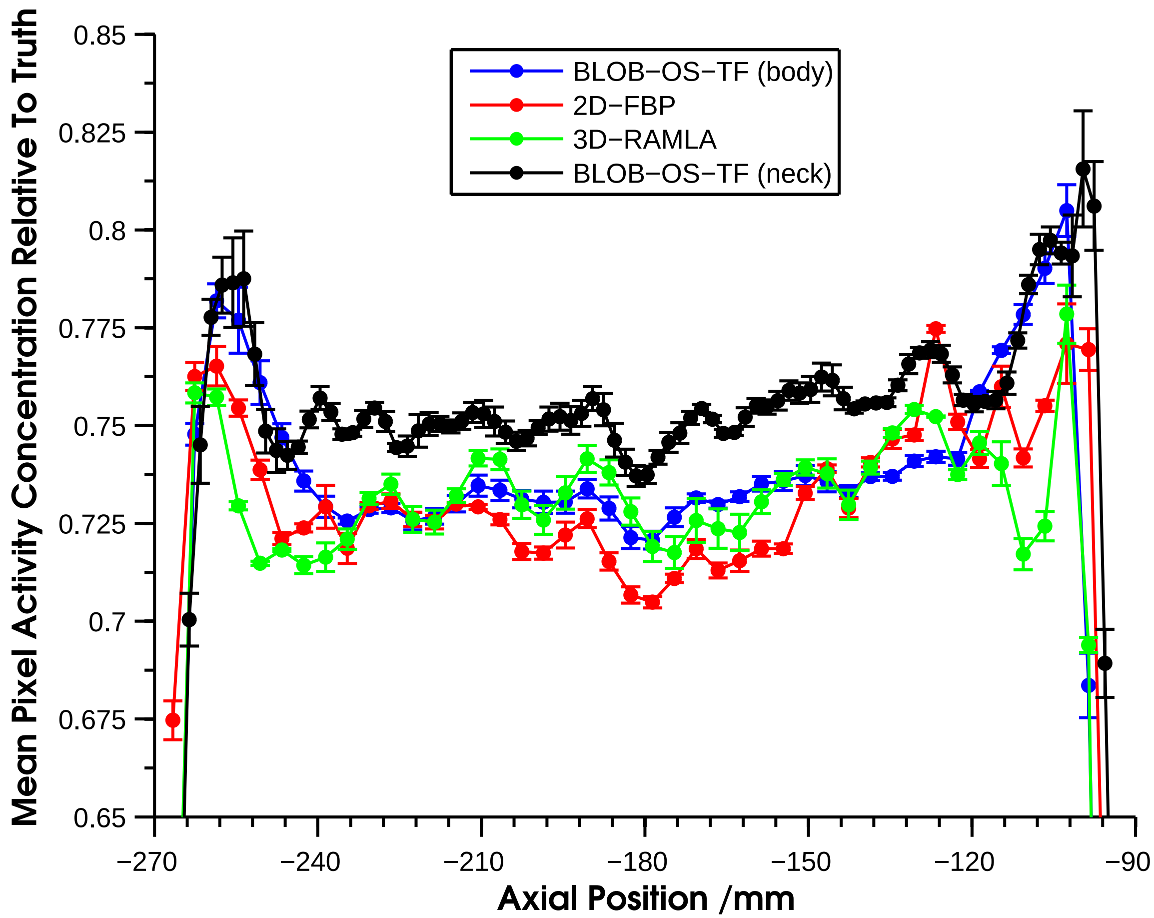
^{68}Ge Phantom

Epoxy

Preliminary Results for Large-Volume (9 L) Solid ^{68}Ge phantom

- Dimensions
  - 20 cm diameter
  - 30 cm length
  - density 1.16 g cm^{-3}
- Uniform activity concentration directly traceable to NIST standards with standard uncertainty 1.1%
- Concentration at mid-point of scanning was ~7.2 kBq g^{-1}
- Will be used to monitor performance of multiple scanners during clinical trials – first time with traceable standards!

Mean Axial Activity Profile for 3 to 5 repeated PET/CT scans



Other Phantoms At NIST

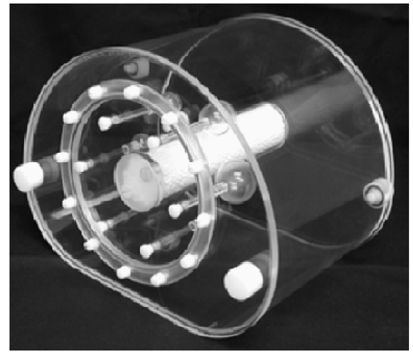
<u>**Anthropometric Phantoms**</u>

- **Simple, well-defined geometry**
  - cylinders, spheres, rods
  - easy to reproduce and standardize
- **Fill with known radioactivity**
  - short-lived (^{18}F) = reusable
  - longer-lived (^{68}Ge) = single study
- **Can scan multiple times**
  - scanner quality control
  - direct comparison between sites

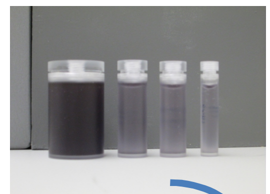
<u>**Anthropomorphic Phantoms**</u>

- **Offer improved realism**
  - truthful body/organ shapes
  - tissue equivalent materials
  - model non-uniform photon attenuation and scattering

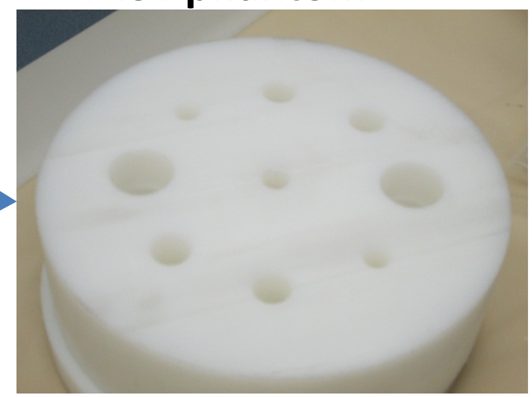
NEMA Image Quality



Jaszczak Cylinder



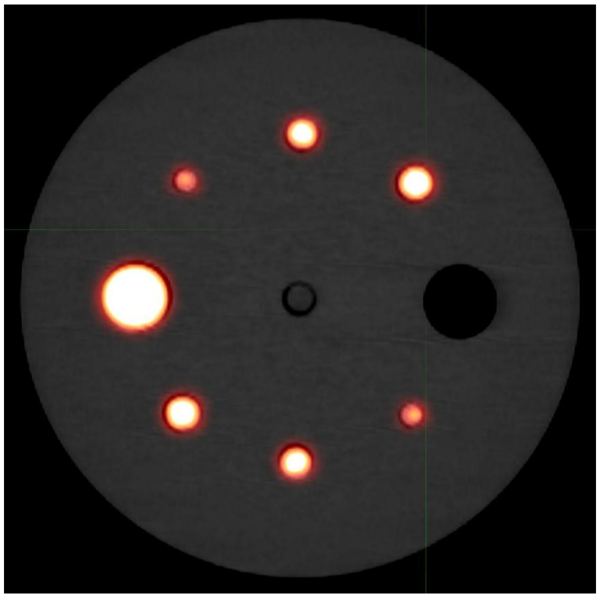
NIST phantom

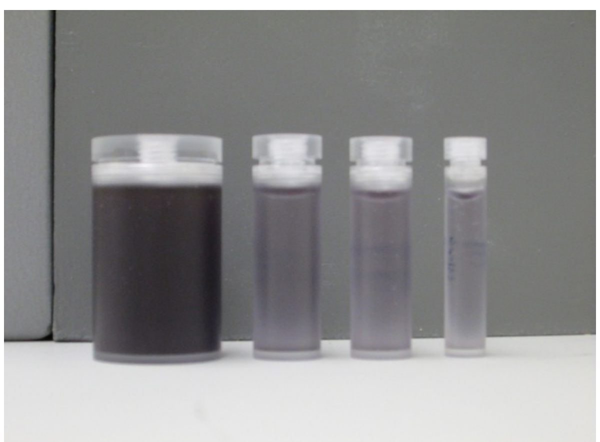


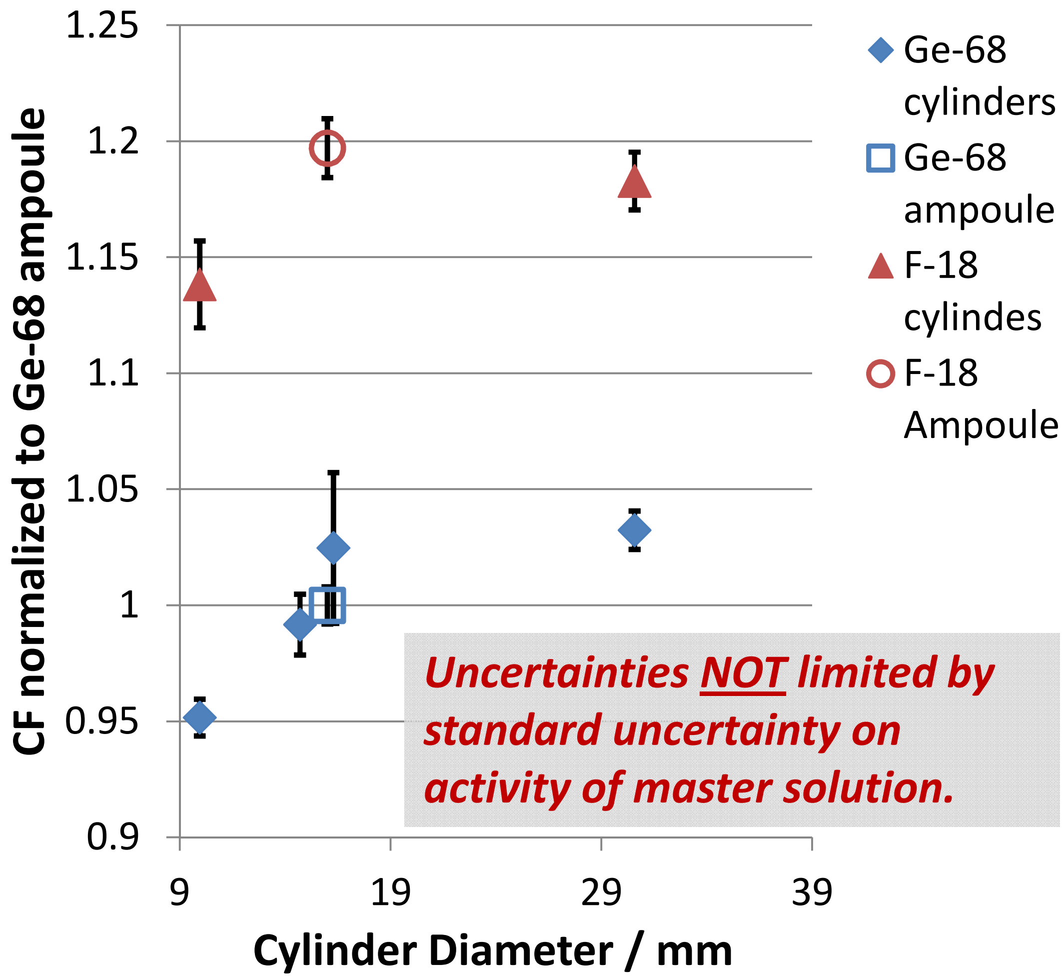
RANDO phantom

Custom phantoms via Rapid Prototyping

Recovered Activity in PET Image of Cylindrical Phantom Inserts







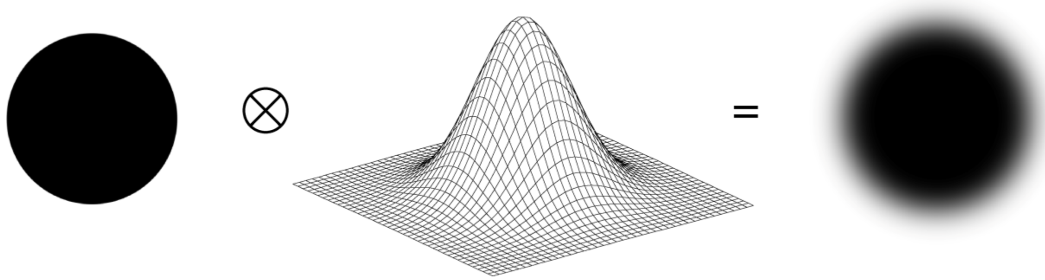
Uncertainties <u>NOT</u> limited by standard uncertainty on activity of master solution.

Development of Corrections for the <u>Partial Volume Effect</u> (PVE)

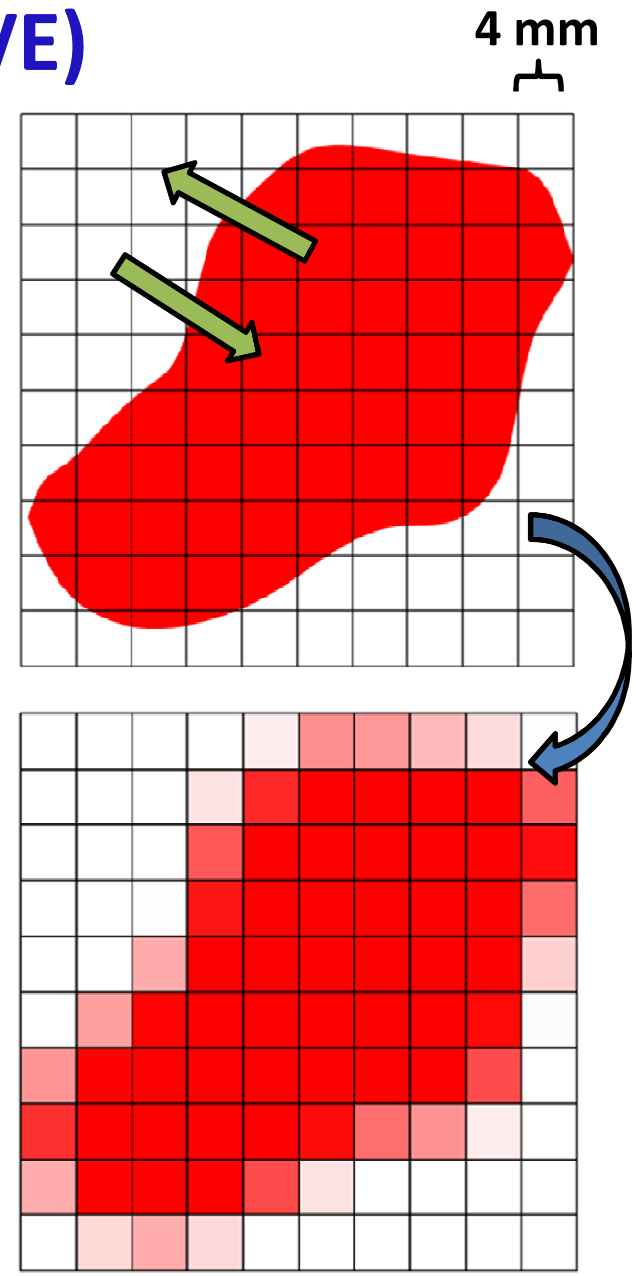
Arises from the poor spatial resolution:

1) Spreading of counts across physical tumor boundaries due to image blurring
2) Tissue fractionation due to coarse voxel grid

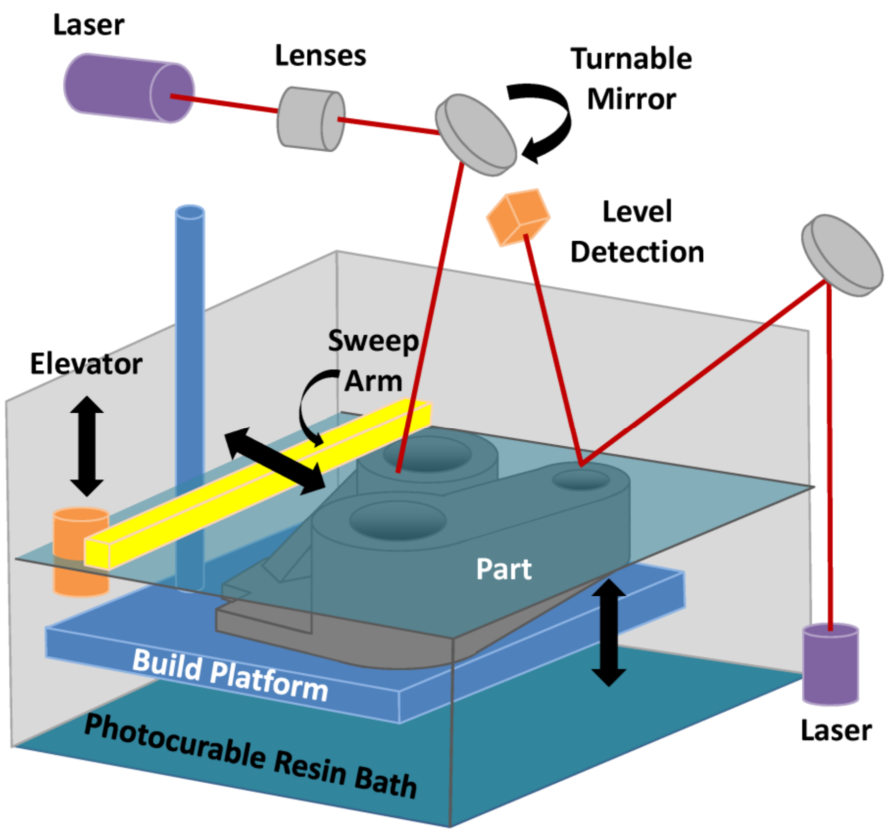
- *General tendency is to make small lesions appear less metabolically active*
- *Strongly dependent on tumor volume and tumor-to-background activity ratio*



True Image **Gaussian Point-Spread Function** **Measured Image**



Rapid Prototyping Custom PET Phantoms For Partial Volume Correction



U.S. Army Benét Laboratories

3D Systems Viper II SLA

- X,Y resolution 0.076 mm (0.003'')
- Z resolution 0.15 mm (0.006'')

Post-processing

- Excess resin removed with solvent
- Cure parts in UV oven

Mirror-guided laser scans liquid photopolymer bath

Stereolithographed Phantoms

- Viper si2 SLA
- 6 phantoms fabricated in ~3 hours
- Dimensions verified with Vernier caliper (± 0.25 mm of design values)
- Translucent photopolymer facilitated filling with radioactivity
- Phantoms did not leak with wall thickness of 1 mm
- Tissue-equivalent (ρ=1.12 g/cm^3, CT # ≈ 200 HU)

Ellipsoid Phantoms

Decreasing Volume →

Volumes: 0.5 to 26 cm^3

Major-to-Minor Axis Ratio: 1:1, 4:3, 8:5, 2:1

Necrotic Sphere Phantoms

Increasing Core Diameter →

Outer Chamber Diameter: 28 mm

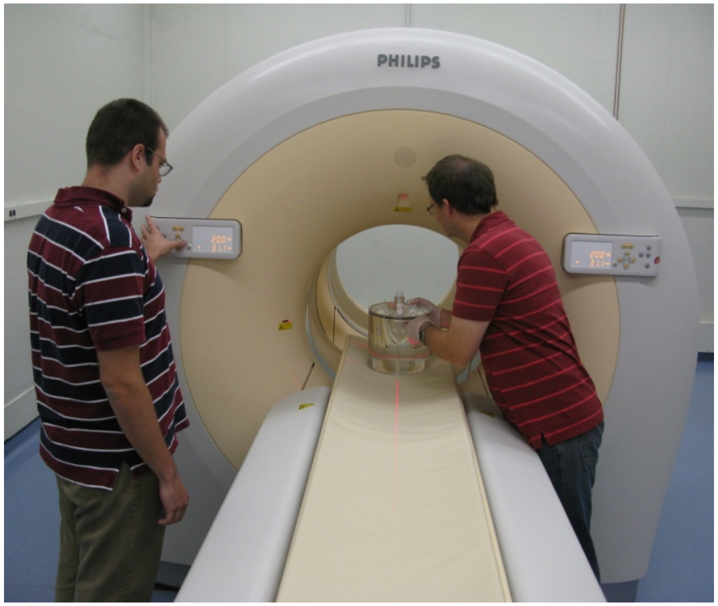
Inner Chamber Diameter: 0, 6, 14, 21 mm

Preparation of Phantoms with Radioactivity To Study Tumor Shape Effect

- Gravimetrically filled phantoms with ^{18}F
- Attach 8 tumor phantoms into Jaszczak cylinder simulating human torso
- Cylinder filled with lower activity concentration of ^{18}F to simulate "hot" lesions in "warm" background
- Activity measurements made using a dose calibrator traceable to NIST primary radioactivity standards
- Uncertainty in the massic activity of the prepared solutions was ~1.2% (k=2)

Experimental Methods:

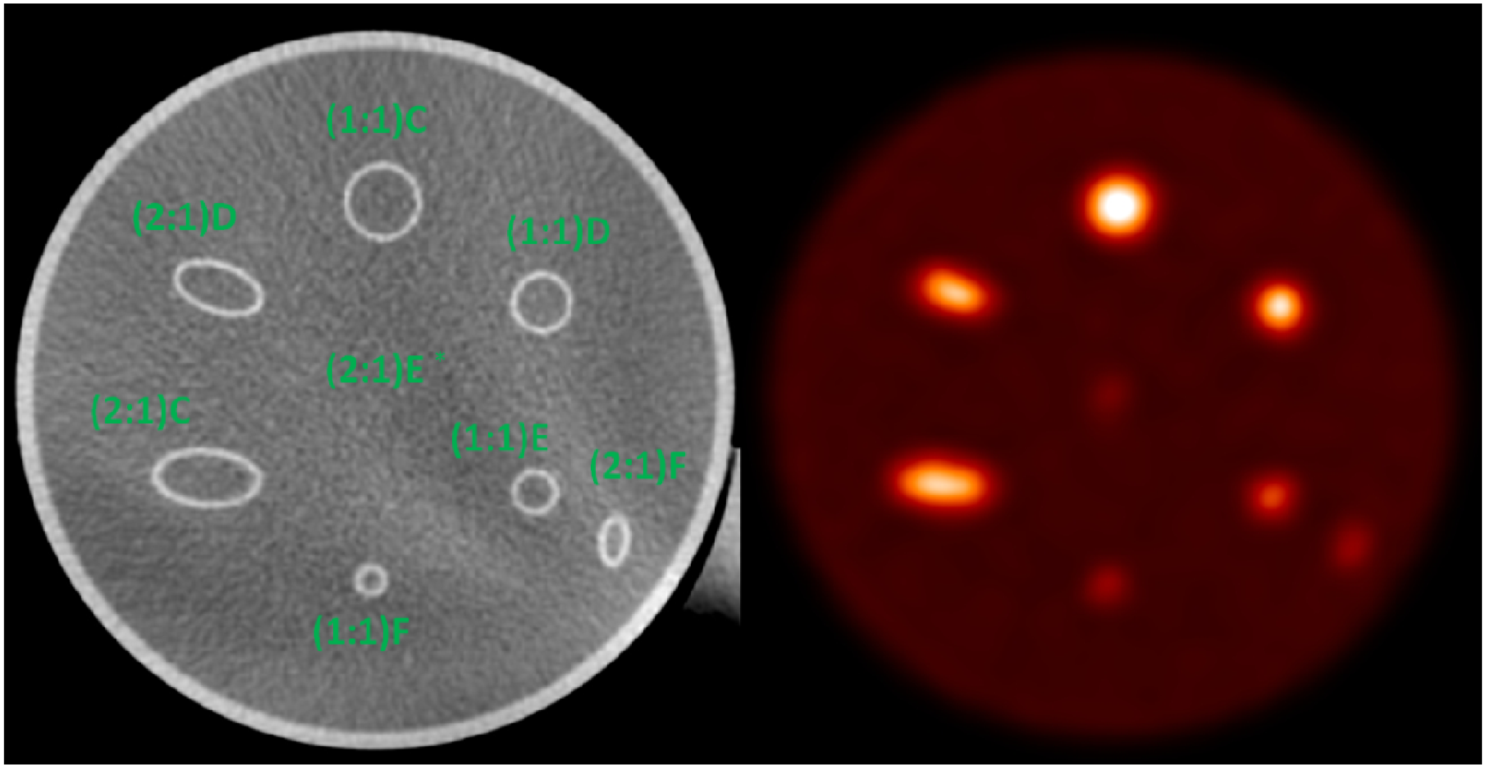
PET/CT Image Acquisition



- Jaszczak cylinder centered in gantry with lasers
- Repeated PET scans acquired using BODY and HEAD protocols
- New CT prior to each PET scan for attenuation correction
- Counting time per scan
  - initially 5-10 min (clinical)
  - later increased to $\geq$ 30 min (better statistics)
- Typical activity concentrations in cylinder at time of first scan were
  - 120 kBq/g (tumor phantom)
  - 15 kBq/g (background)

Experiment #1 Results:

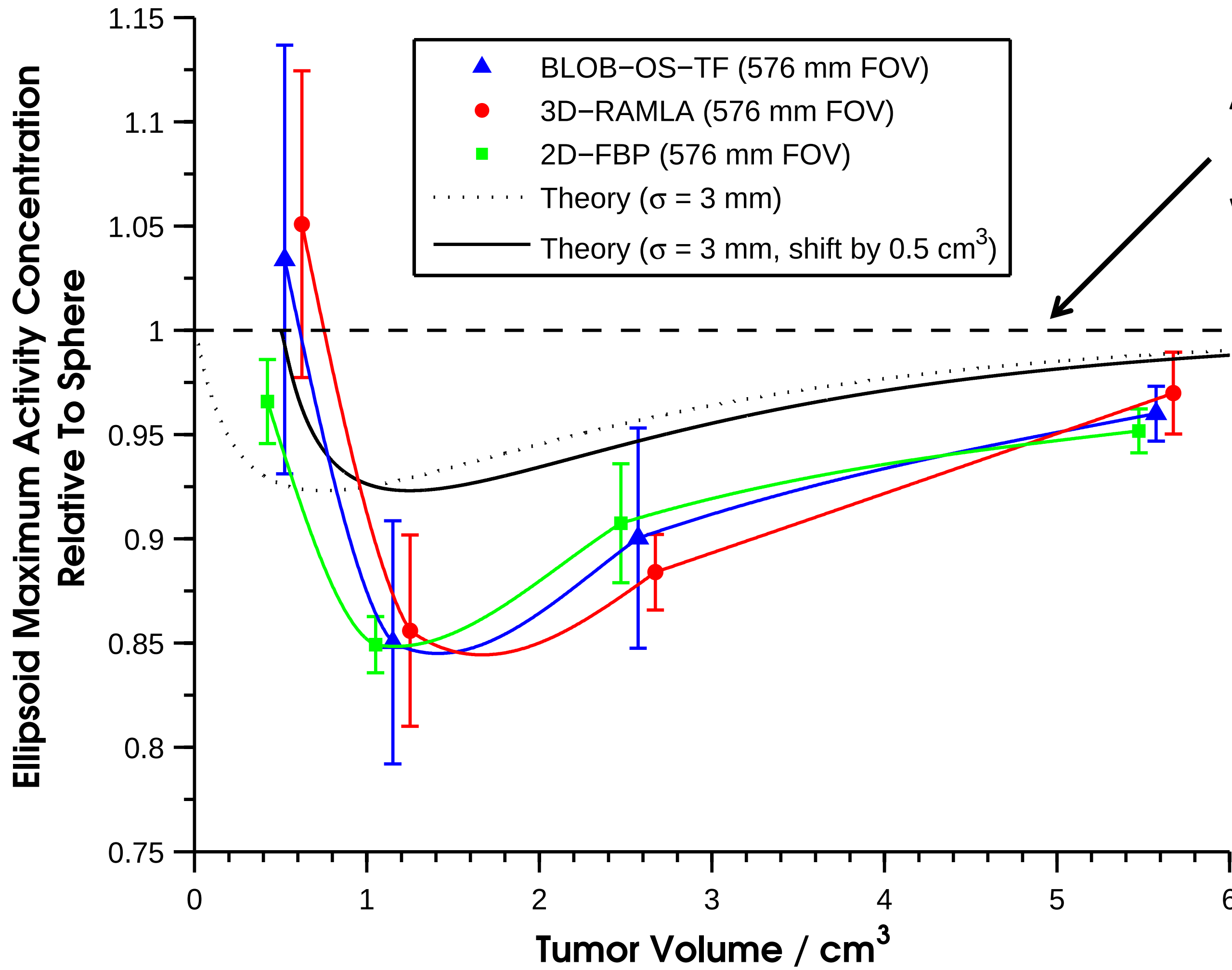
Comparison of Ellipsoids Axis Ratio 2:1 to Spheres



- Jaszczak cylinder contained 4 ellipsoids and corresponding spheres with identical volume and activity concentration
- Volumes ranged from 0.5 to 5.6 cm^3
- Tumor-to-background activity concentration ratio was 9.07:1
- 4 PET/CT scans acquired with counting times ≥ 30 min

Experiment #1 Results:

Tumor Shape Effect for Ellipsoids Axis Ratio 2:1 (**ROI Max**)

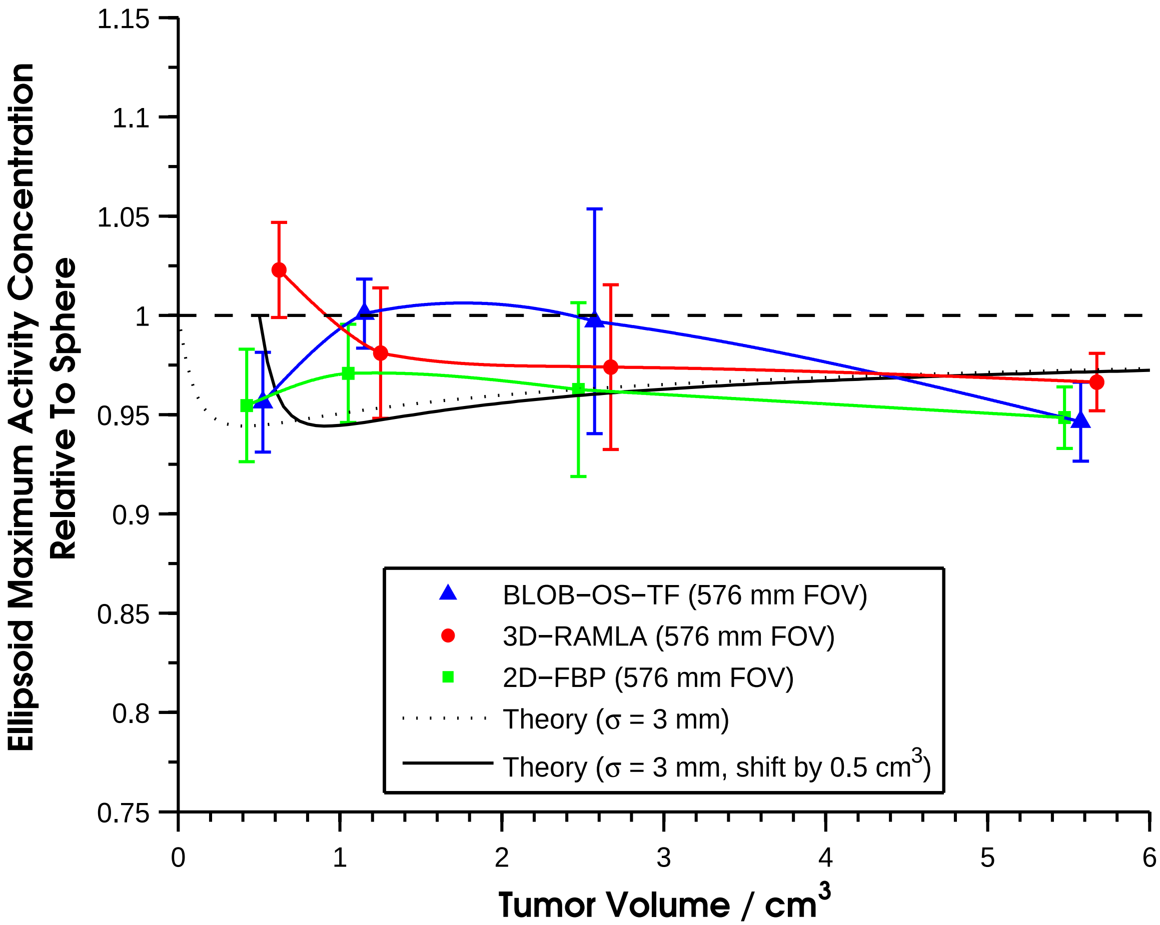


Assumes Scanner PSF is Gaussian with σ = 3 mm

15% difference in ROI maximum between spheres and ellipsoids observed for the tumor phantom with volume 1.15 cm^3

Experiment #1 Results:

Tumor Shape Effect for Ellipsoids of Axis Ratio 2:1 (ROI Mean)

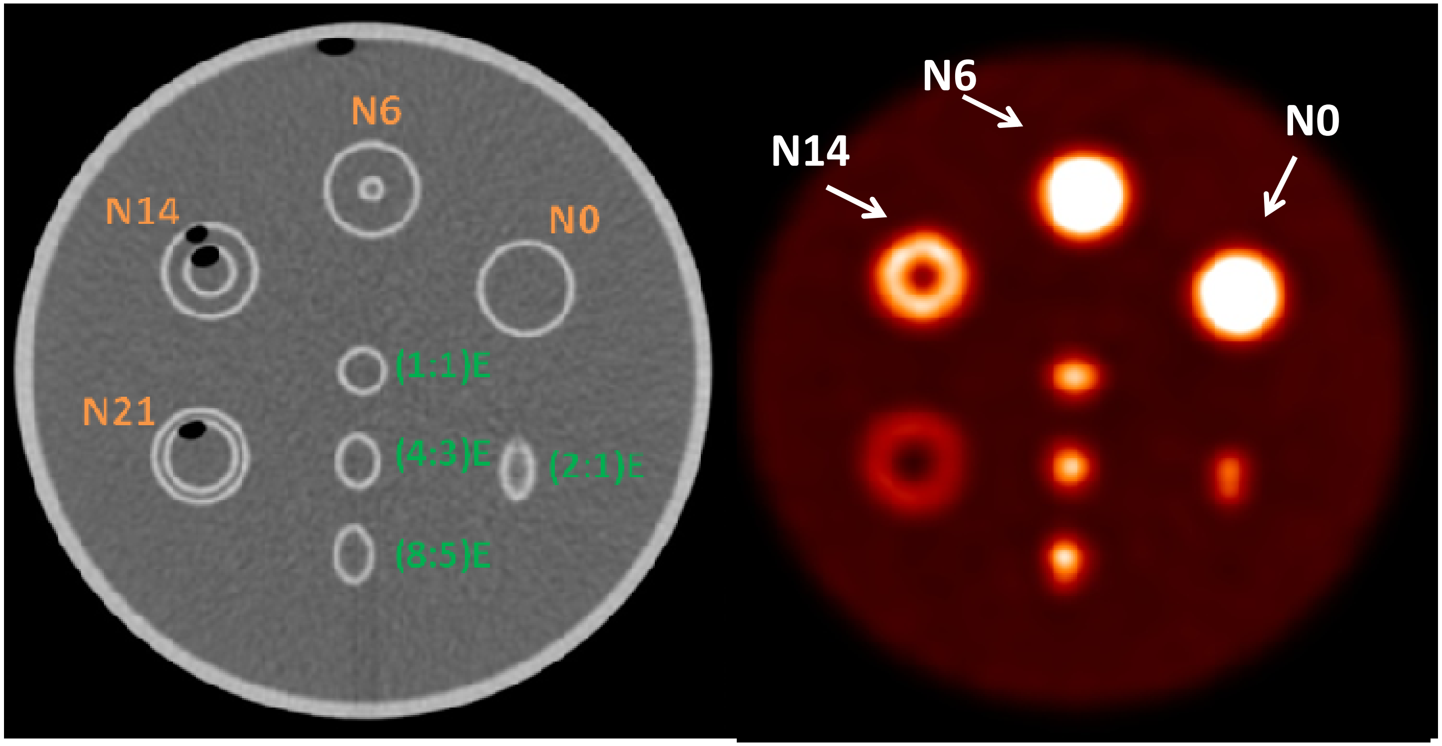


No clear difference between ROI means of the ellipsoids and spheres

That the shape effect is not evident might be explained by a voxel grid effect

Experiment #2 Results:

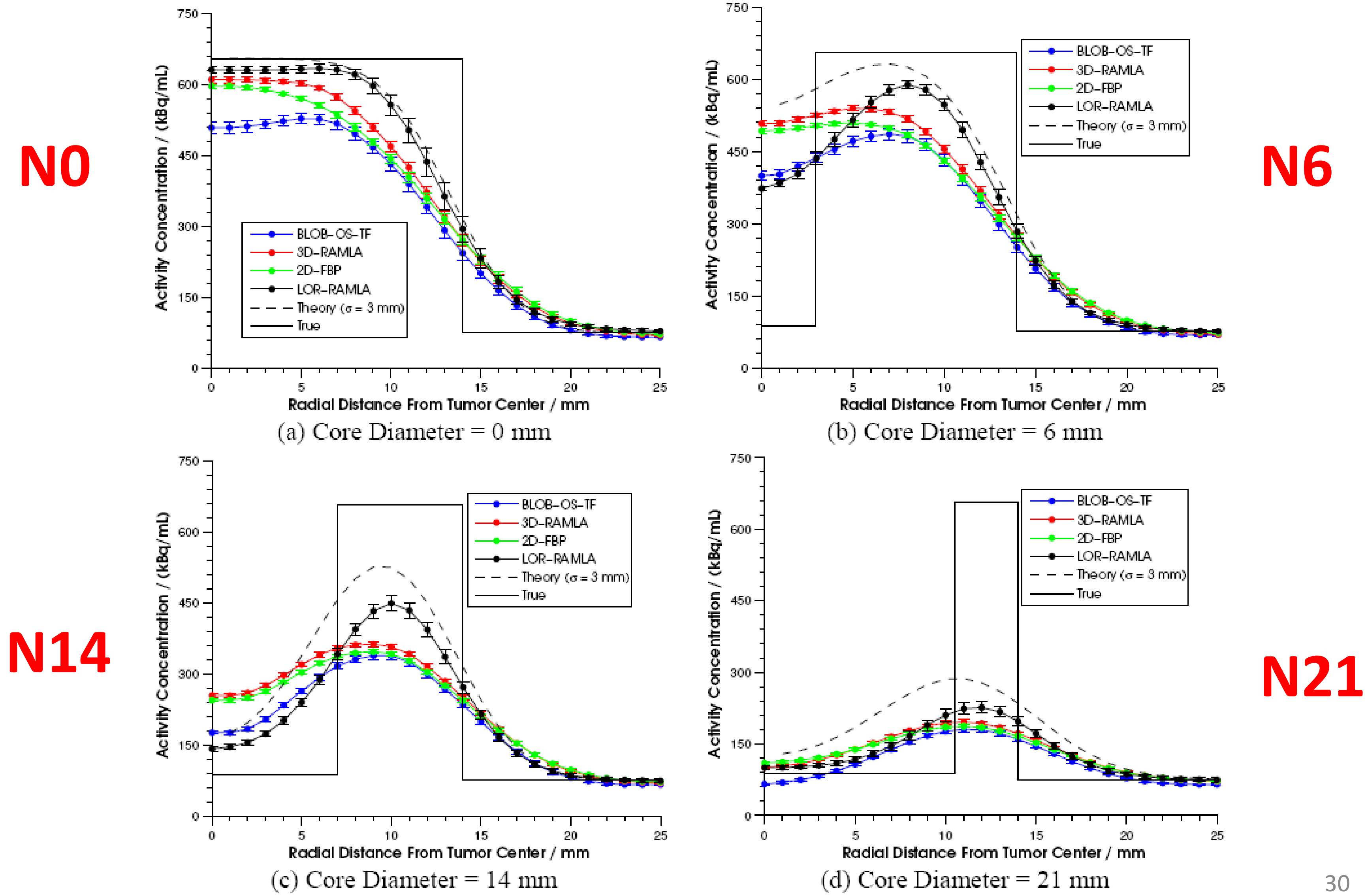
Necrotic Phantoms & Ellipsoids of Different Axis Ratio



- Jaszczak cylinder contained:
  - 4 necrotic phantoms with different core diameter
  - 4 ellipsoids of volume 1.15 cm^3, but different axis ratios (1:1, 4:3, 8:5, 2:1)
- Tumor-to-background activity concentration ratio was 8.73:1
- Rim-to-core activity concentration ratio was 7.48:1
- A total of 16 PET scans acquired with counting times of 5 to 9 min

Experiment #2 Results:

Radial Profiles Of Necrotic Core Phantom Images



(a) Core Diameter = 0 mm

(b) Core Diameter = 6 mm

(c) Core Diameter = 14 mm

(d) Core Diameter = 21 mm

Clinical Discussions

• Current practice of oncology focuses on tumor endpoints of "reduced volume" or "reduced metabolism."

i.e., the shape of the tumor is not clinically significant

• Proposed PET Response Criteria (PERCIST) define a 30% change in the SUV value as being clinically relevant

• Experiment #1 showed a change in tumor shape alone can give rise to an apparent tumor response half this size—without any change in volume or metabolic activity

• A correction for the tumor shape effect is desirable to avoid bias in the measured radioactivity

• Unfortunately, the magnitude of the shape effect was comparable to the repeatability of the PET measurements (~5-10%)—corrections will be difficult

• The phantom experiments were highly controlled, even larger uncertainties expected in a clinical scan of a live patient

Summary

- NIST has a dedicated laboratory for the development of standard sources & methods to facilitate traceability of ^{18}F-FDG PET measurements to SI units (Bq/mL)
- Standards for ^{18}F will be disseminated to clinical sites using ^{68}Ge, a long-lived surrogate isotope
- We are measuring phantoms of different geometries on a suite of instruments at our disposal
- We are quantifying the components of the overall uncertainty in PET measurements, while seeking ways to improve accuracy
- These tools are expected to have important applications for clinical trials, and also dosimetry for radionuclide therapy

What are the future opportunities?

- Phantoms and standards for PET/MR
  - NIST Boulder is working on standards for MR
- Use rapid prototyping to improve realism of existing physical phantoms by **fabricating** new phantoms using patient-images.