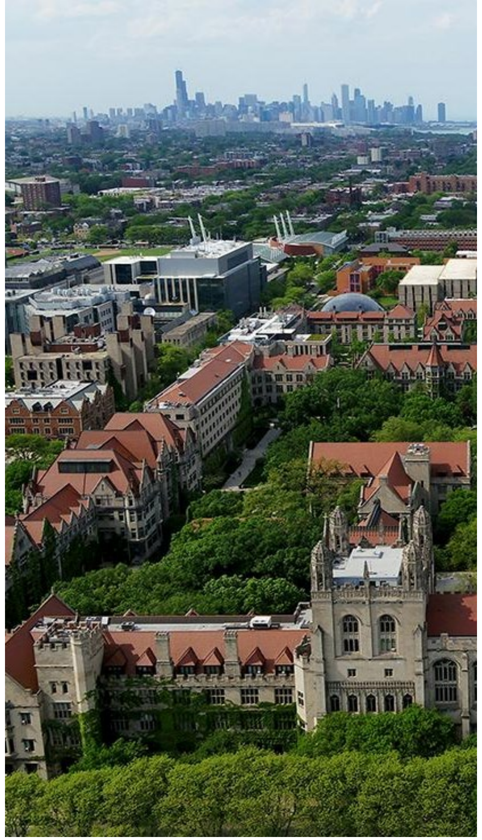
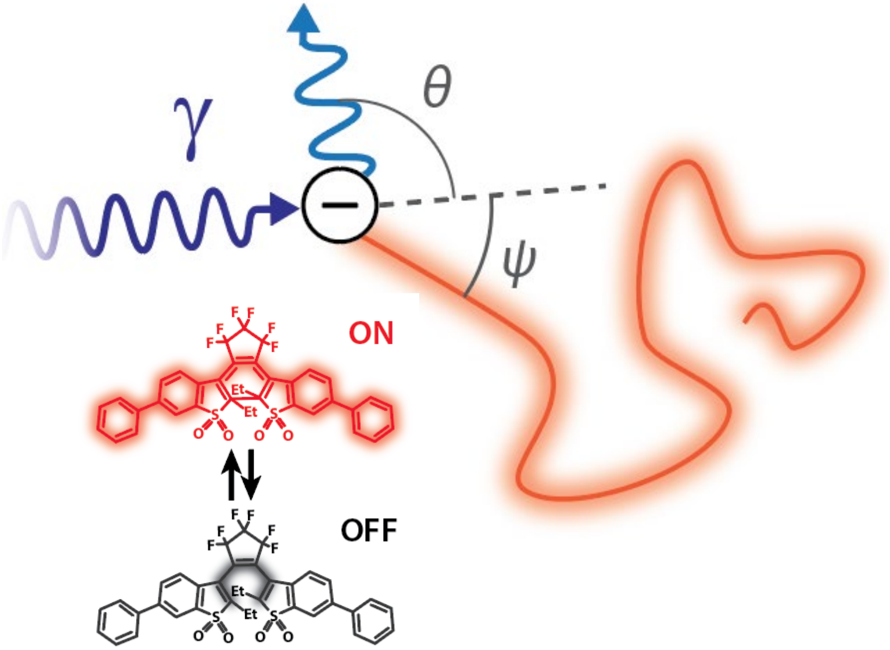


Detecting Compton Scatters in Liquid Media for Low-Dose High-Resolution TOF-PET

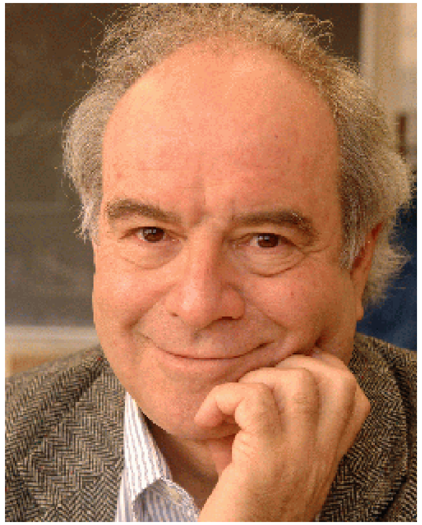
Allison H. Squires
Neubauer Family Assistant Professor
Pritzker School of Molecular Engineering
University of Chicago
Web: squireslab.uchicago.edu



DOE-NIH Workshop:
Advancing Medical Care through Discovery in the Physical Sciences: Radiation Detection
March 16th, 2023 · Jefferson National Accel. Facility

SQUIRES LAB

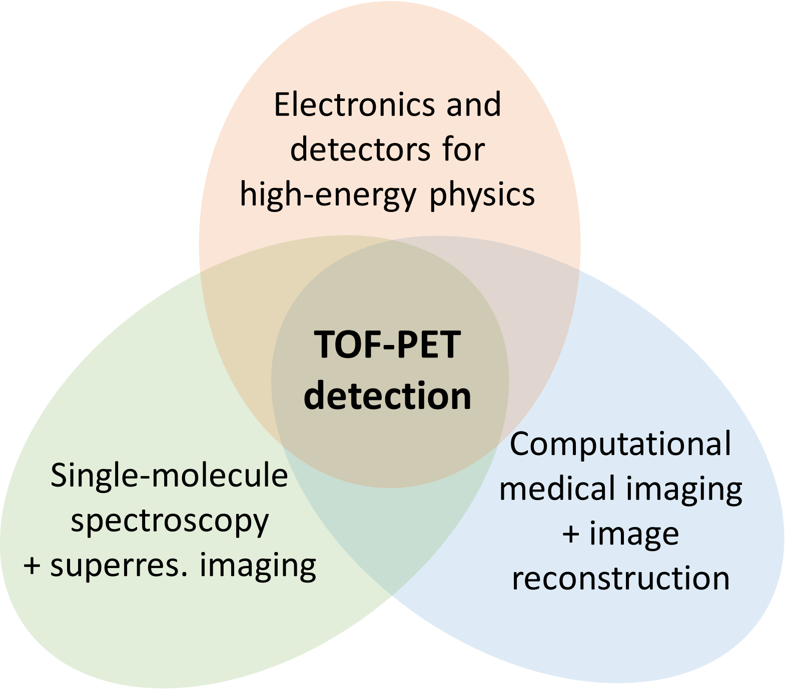
ACKNOWLEDGEMENTS: Our cross-disciplinary team @ University of Chicago



Henry Frisch
Physics

Patrick La Riviere
Radiology

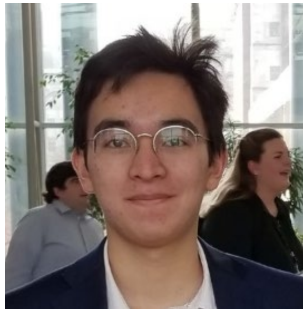
Allison Squires
Molecular Engineering



UNDERGRADUATES

Kepler Domurat-Sousa

Maya McDaniel



João Shida

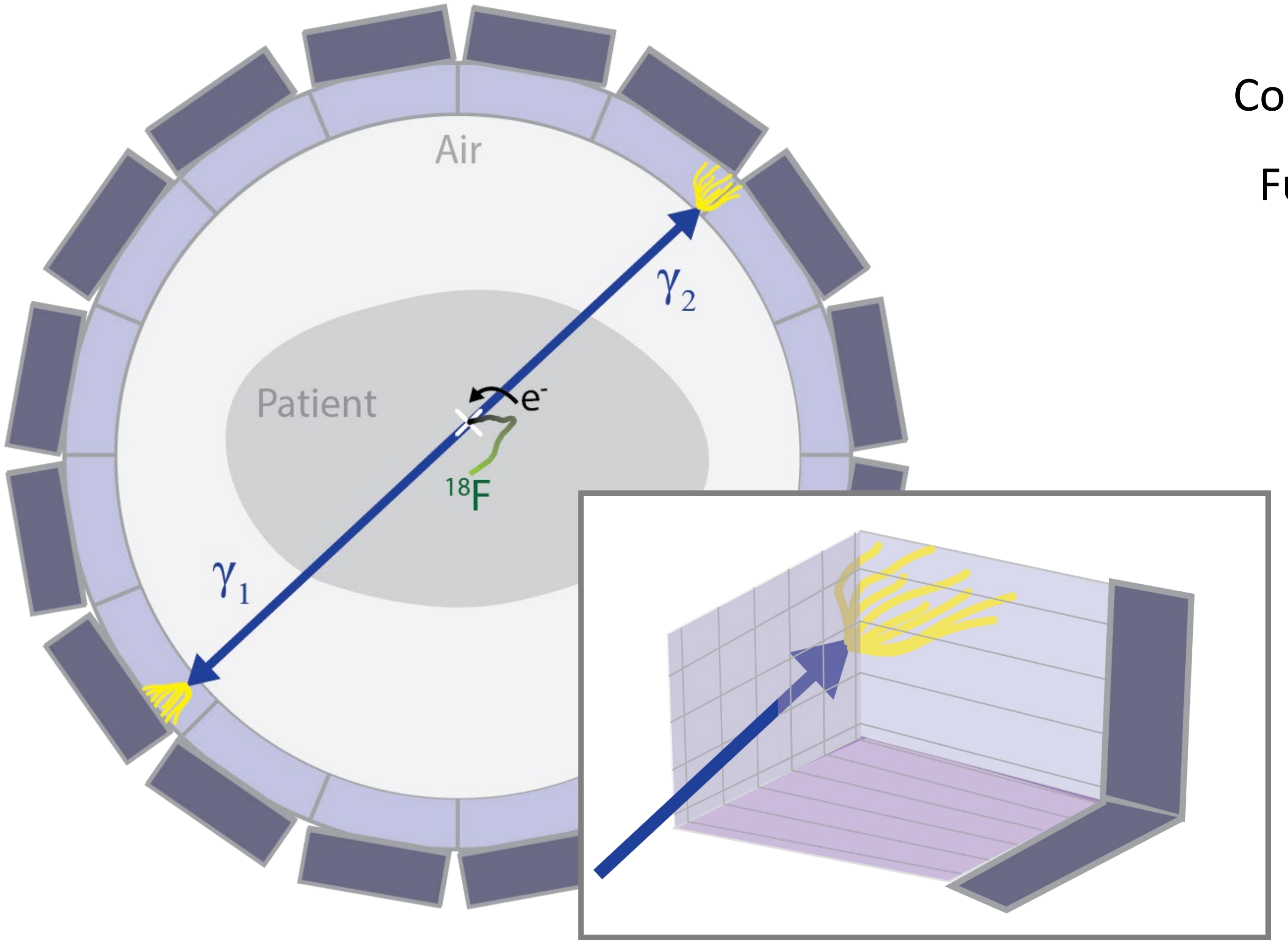
Eric Spieglan

Cameron Poe

Special thanks:
Dr. Bernhard Adams
Prof. Juan Collar

Fermilab test beam
UChicago Med small animal irradiator

PROBLEM: What are detector-imposed vs. fundamental limitations of TOF-PET?



	Sensitivity	Resolution (FWHM)
Commercial	1-2%	4-5mm
Full-body	10-17%	3-4mm
Ideal	*100%*	*< 1mm*

Higher sensitivity would...

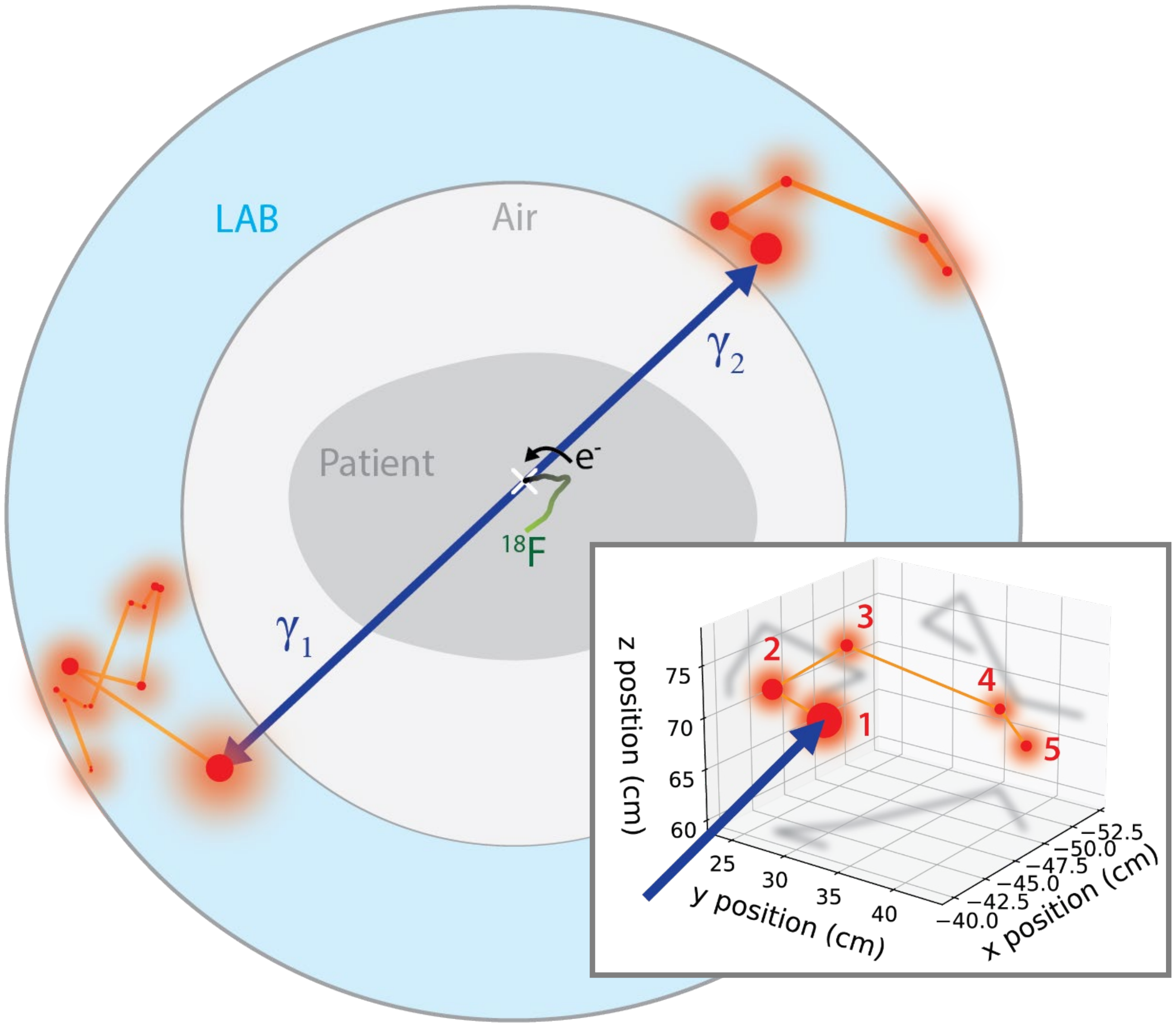
- Reduce radioactive dose to patient
- Decrease imaging time
- Enhance contrast-to-noise
- Expand geographical access

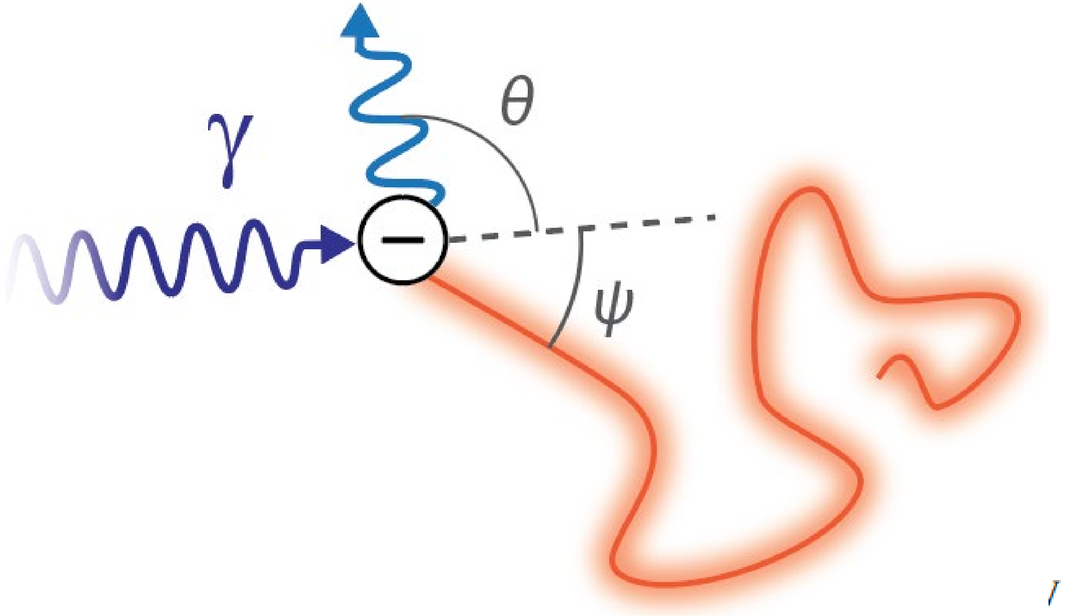
Better resolution would...

- Reveal smaller lesions
- Improve anatomical registration
- Enable new applications

Tiwari… Sunderland (2021) *Med. Phys.*
Spencer… Cherry et al (2020) *J Nucl. Med.*

PROPOSAL: Determine lines-of-response via Compton scattering in low-Z media





Requirements:

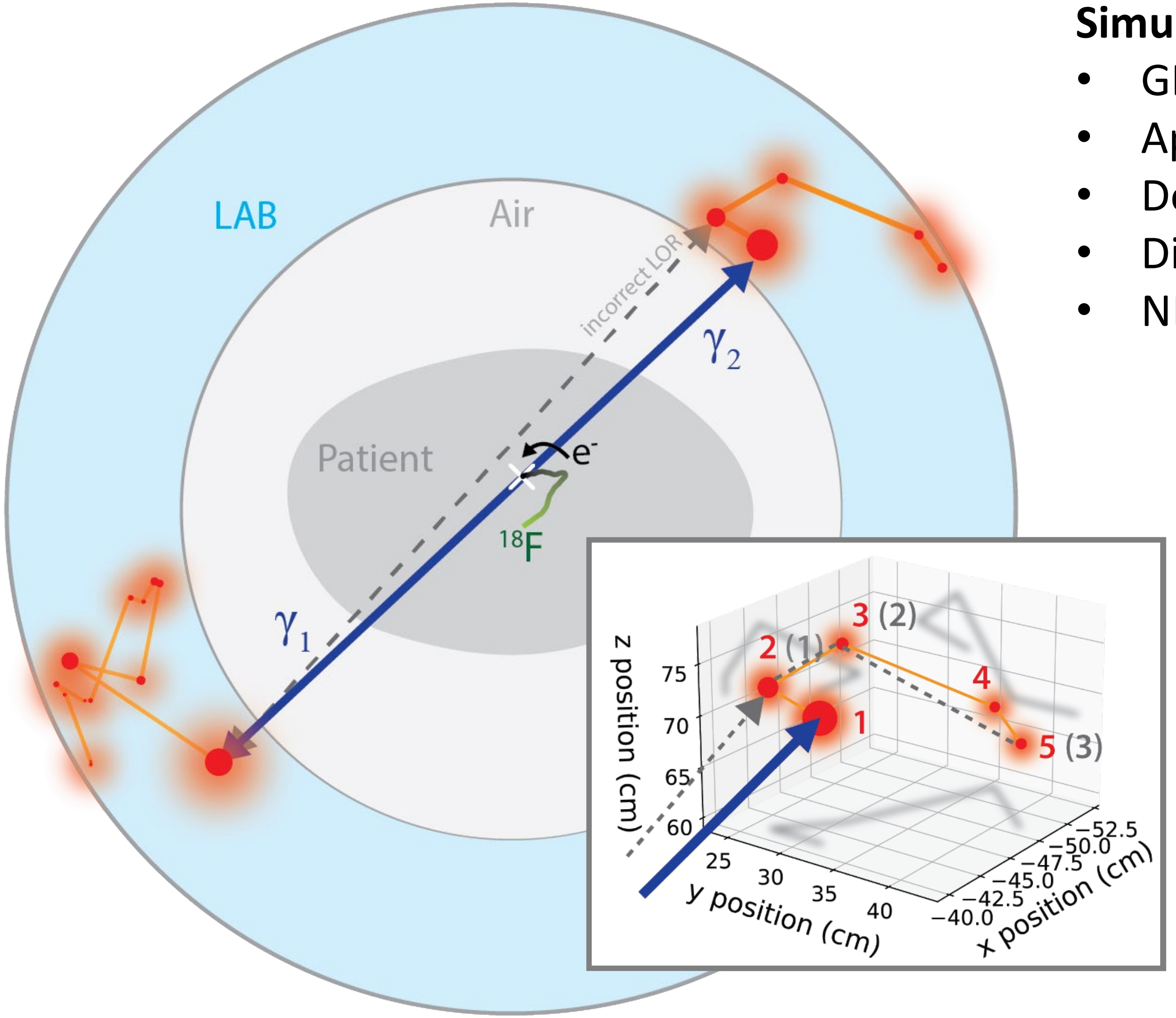
- Determine location, energy of recoil e^-
- Deduce line of response @first scatter

Complications:

- Less energy deposited by e^- at track start
- Multiple Compton scatters in a chain
- Electron trails must be erasable

Shida JF, Spieglan E, Adams BW, Angelico E, Domurat-Sousa K, Elagin A, Frisch HJ, La Riviere P, Squires AH. (2021) *Nucl. Inst. Meth. Phys. Res. A*

SIMULATION: Full TOPAS / GEANT4 Monte Carlo simulation of TOF-PET



Simulation:

- GEANT4 + customized TOPAS to generate ground truth
- Apply parameterized uncertainty to ground truth
- Determine LORs via max. likelihood of scatter ordering
- Direct image reconstruction from LORs
- NEMA NU-2 2018 protocols for resolution, sensitivity

Tunable parameters:

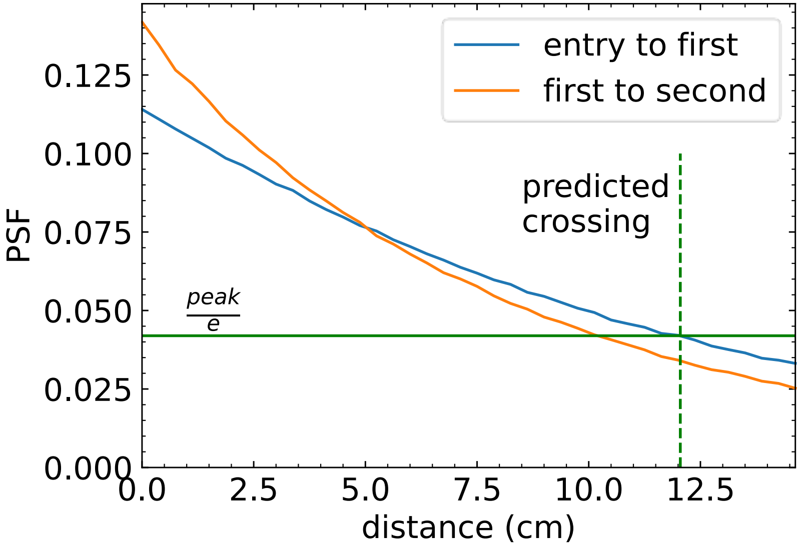
- Spatial resolution (1 mm)
- Energy resolution (1 keV/switch)
- Temporal resolution for TOF (500 ps)

Results:

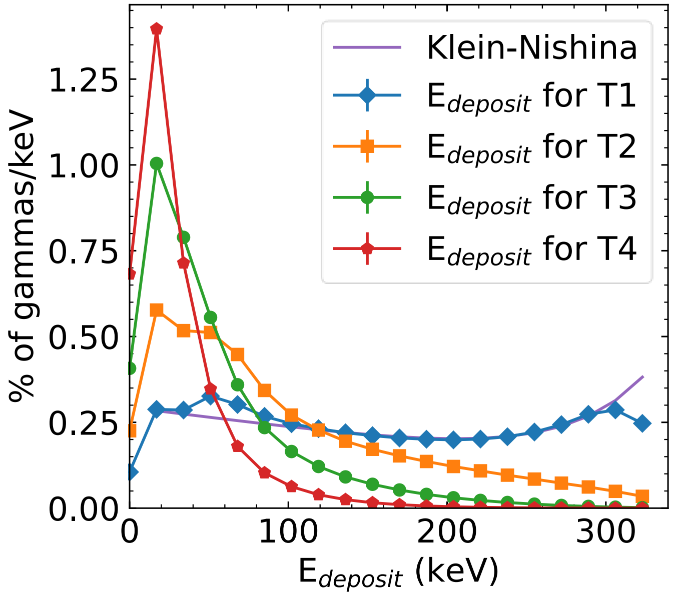
1. Validation
2. Compare to LYSO state-of-the-art
3. Understanding possible pitfalls
4. Determine influence of tunable parameters to set minimum specs for experimental implementation

Shida JF, Spieglan E, Adams BW, Angelico E, Domurat-Sousa K, Elagin A, Frisch HJ, La Riviere P, Squires AH. (2021) *Nucl. Inst. Meth. Phys. Res. A*

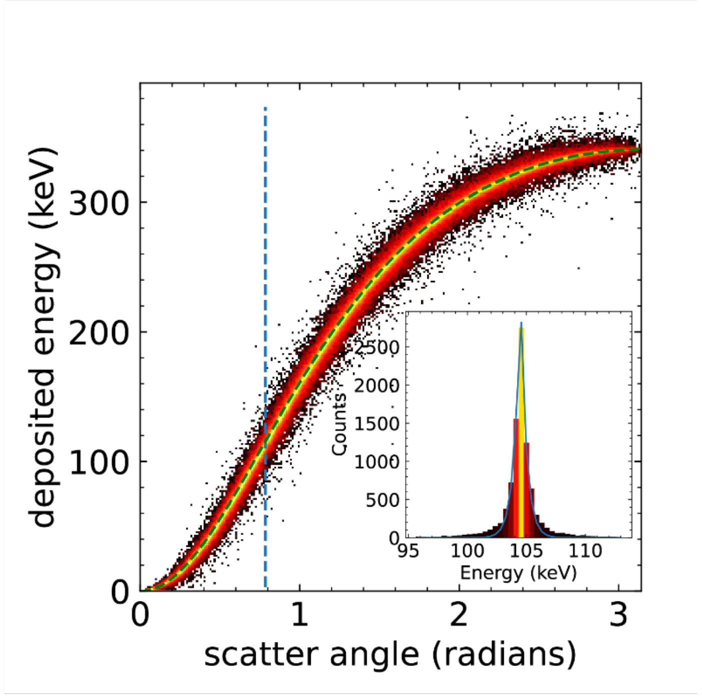
SIMULATION: Validation of simulated data



Linear attenuation:
12.05 cm (first scatter)



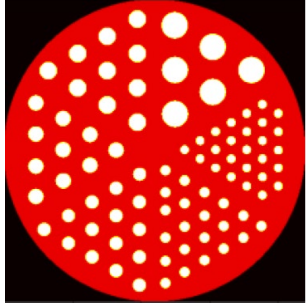
Energy of recoil
electron by scattering
event order
(Klein-Nishina)

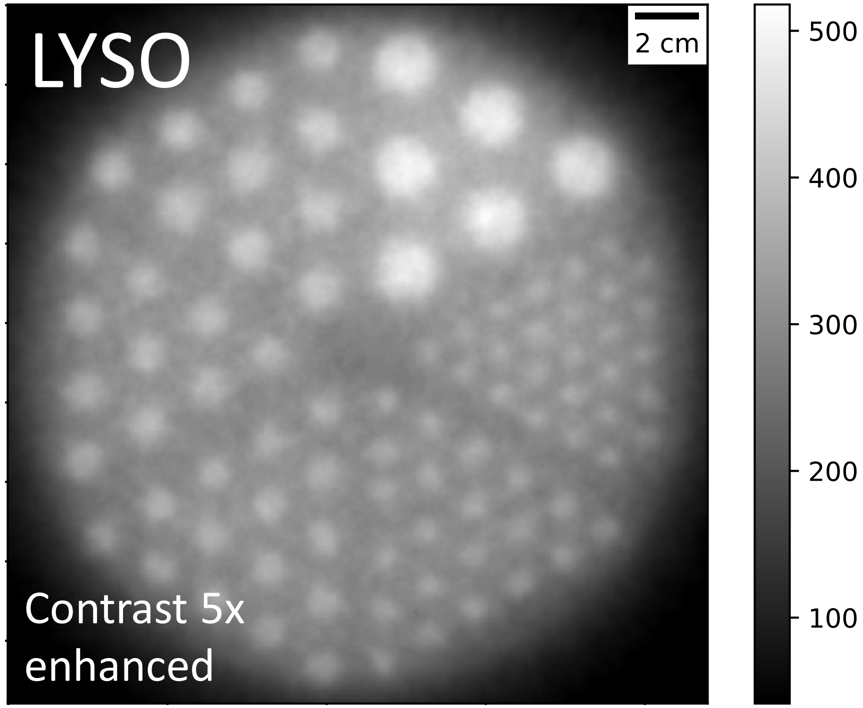


Scattering angle –
energy distribution for
first scatter (K-N)

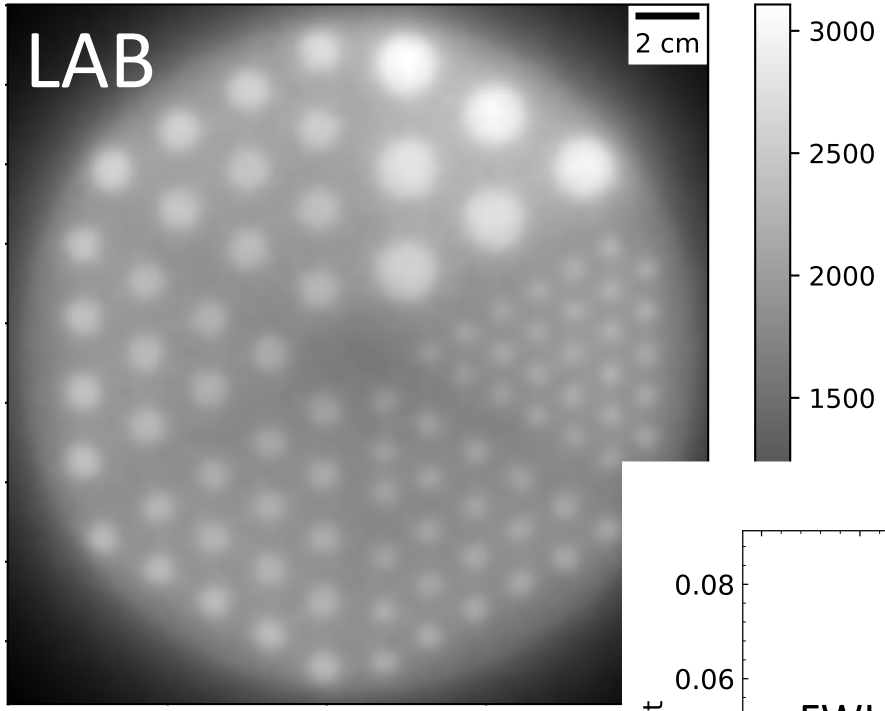
Domurat-Sousa K, Poe C, Shida JF, Spieglan E, McDaniel M, et al. (*unpublished*)

SIMULATION: Sensitivity and resolution of Compton scattering vs. scintillation



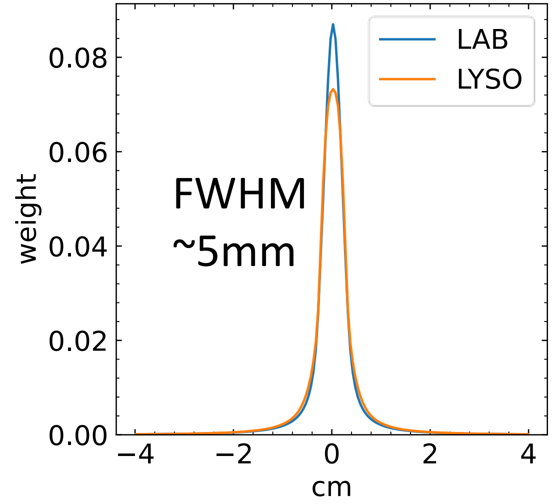


Sensitivity: 15%



Sensitivity: 70%

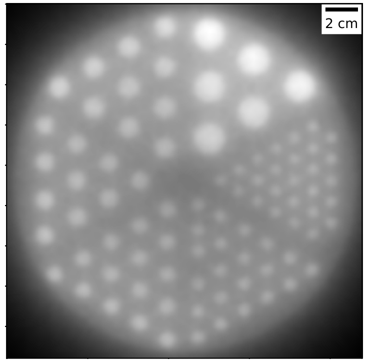
(61.4% correct LOR,
8.8% incorrect)



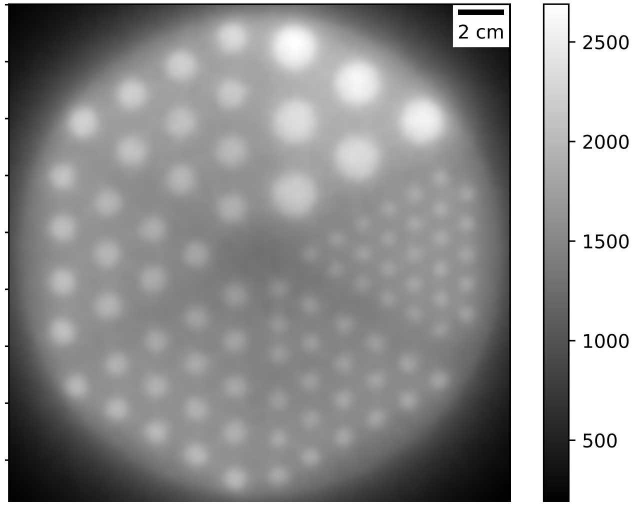
Domurat-Sousa K, Poe C, Shida JF, Spieglan E, McDaniel M, et al. (*unpublished*)

SIMULATION: Not all misidentified Compton scattering chains degrade resolution

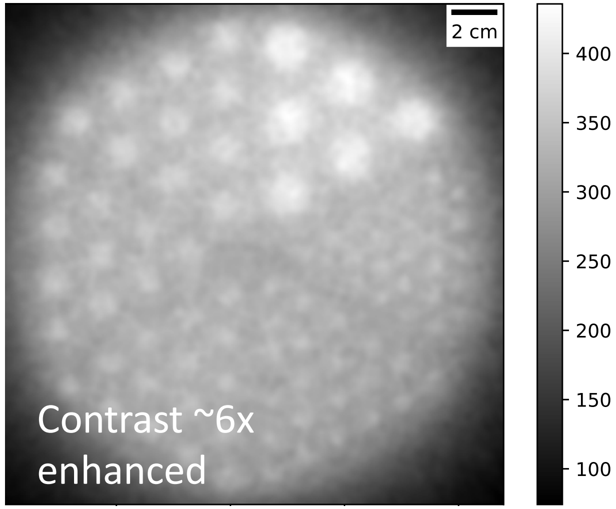
Original image

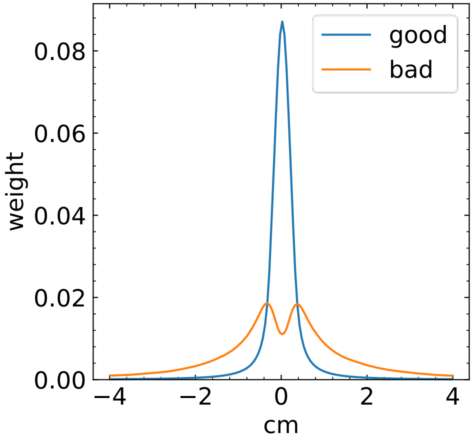


Correct LOR only



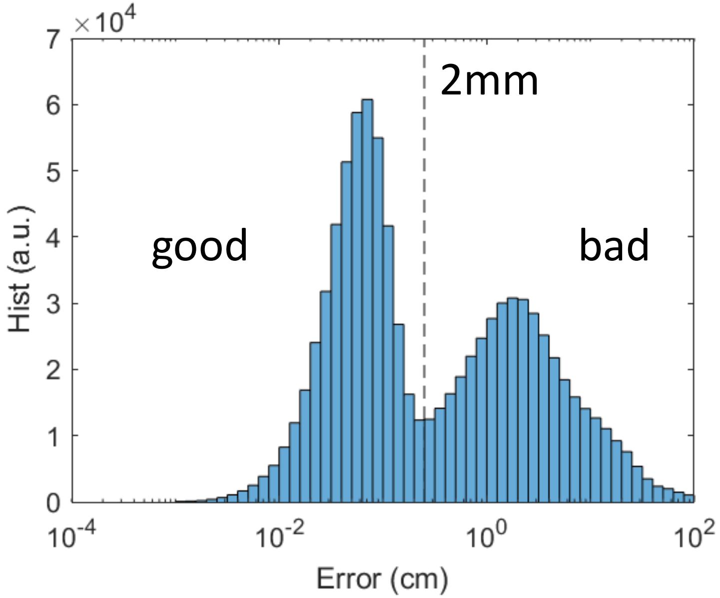
Incorrect LOR only





Misidentifications are bimodal

Small initial scatter or close scatters can result in a “near miss” LOR



Domurat-Sousa K, Poe C, Shida JF, Spieglan E, McDaniel M, et al. (*unpublished*)

SIMULATION: How do spatial and energy resolution influence detector performance?

Energy
Resolution:
1, 10, 100
keV/switch

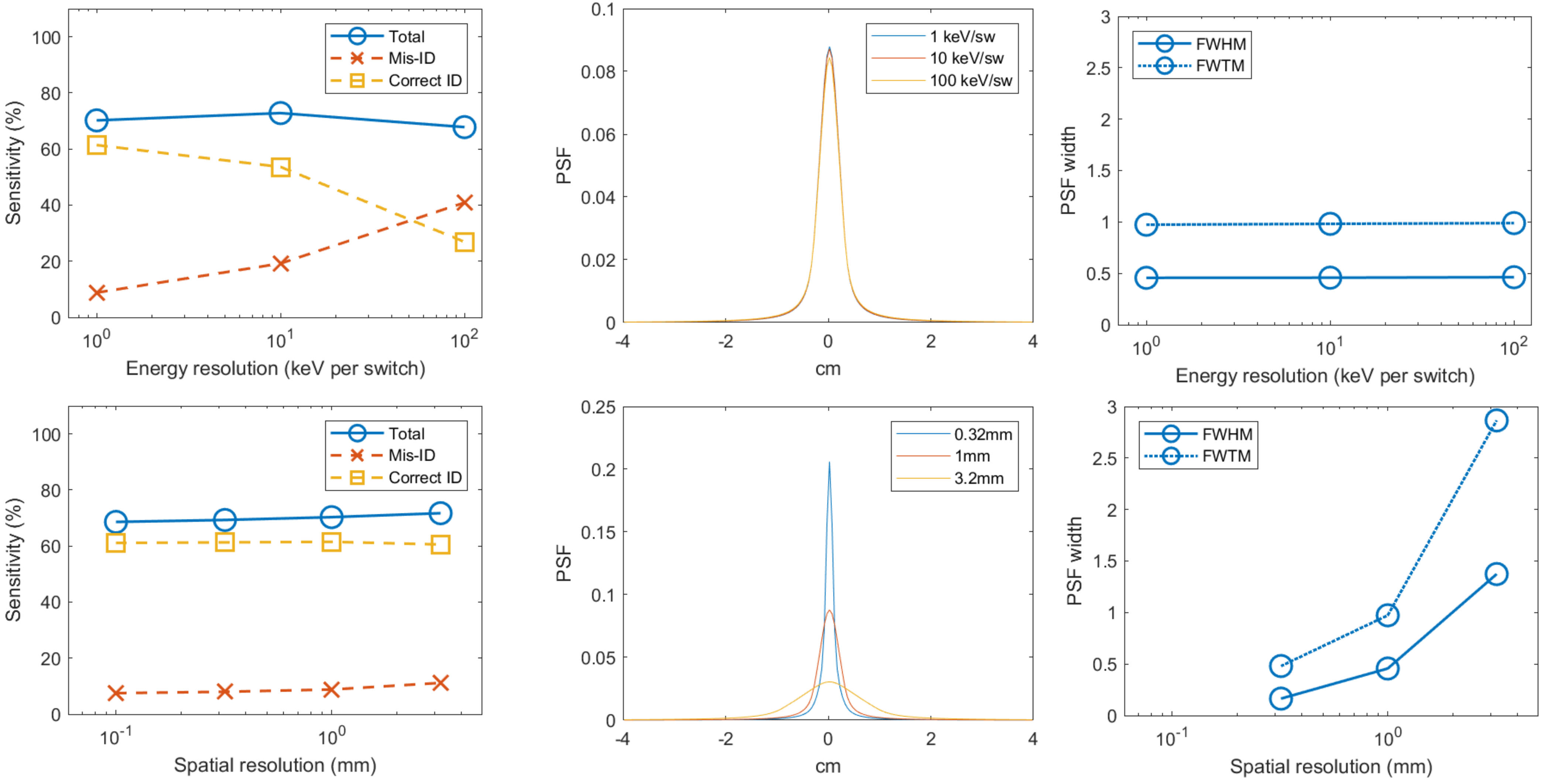
Mostly affects sensitivity

Spatial
Resolution:
0.1, 0.3, 1, 3 mm

Mostly affects resolution

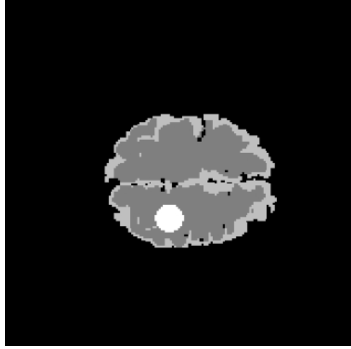
Sensitivity

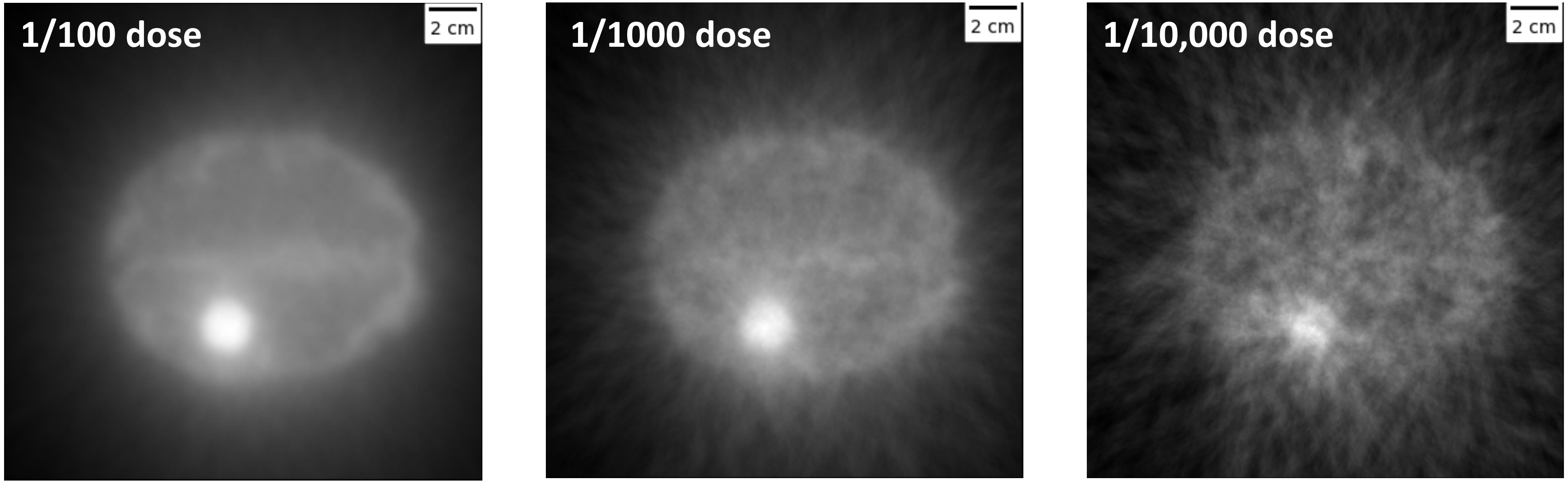
Resolution



Domurat-Sousa K, Poe C, Shida JF, Spieglan E, McDaniel M, et al. (*unpublished*)

SIMULATION: XCAT brain phantom with lesion, down to 1/10,000 dose

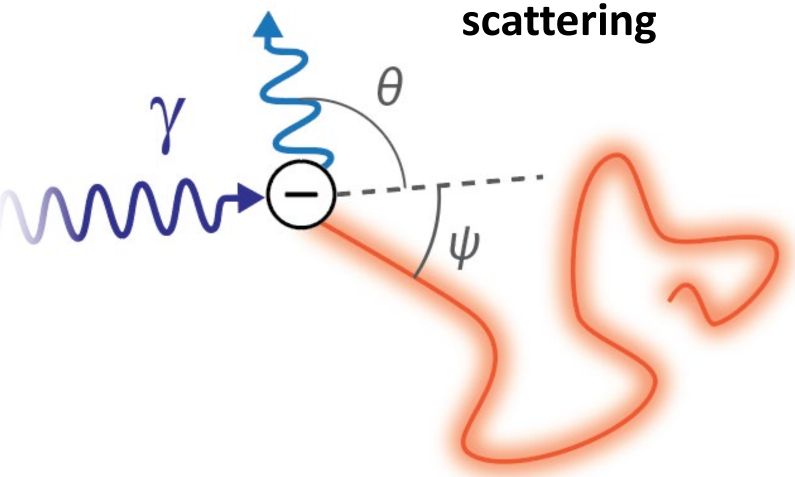




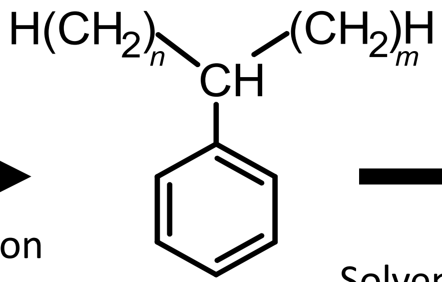
Domurat-Sousa K, Poe C, Shida JF, Spieglan E, McDaniel M, et al. (*unpublished*)

EXPERIMENT: Energy deposited in solvent leaves a temporary "trail"

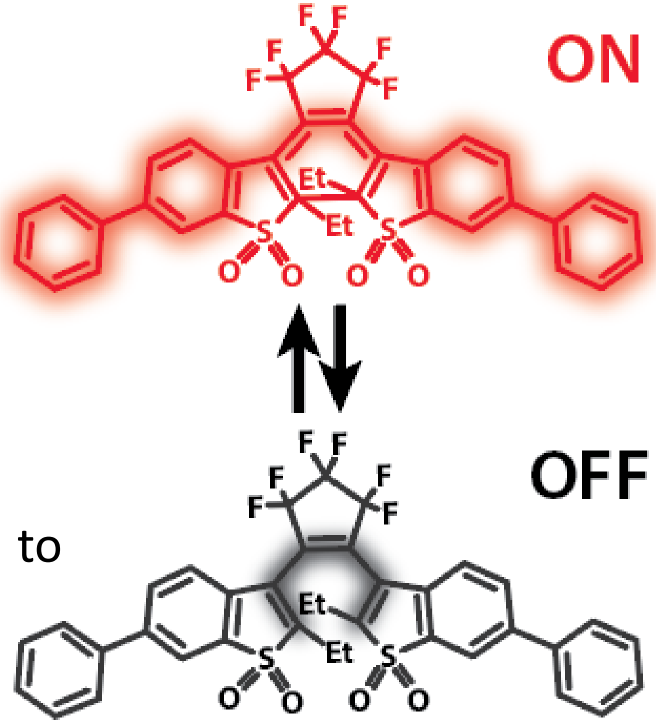
Compton scattering



Low-Z detection media
e.g.: linear alkylbenzene

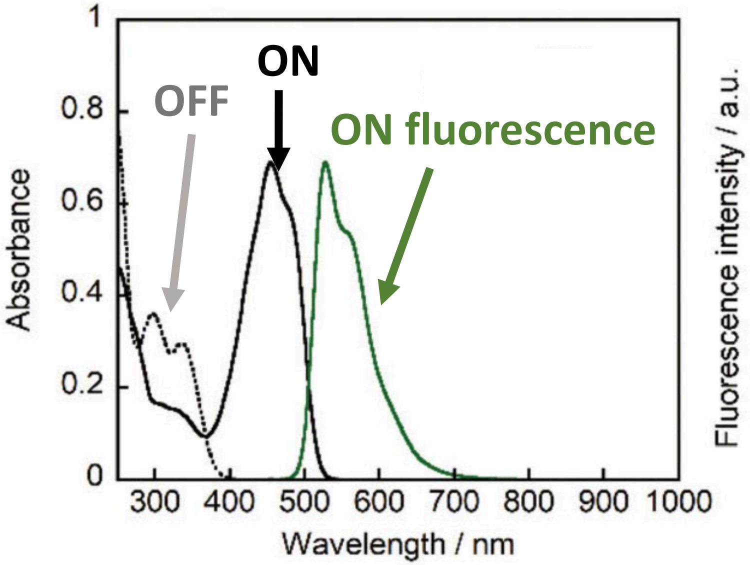


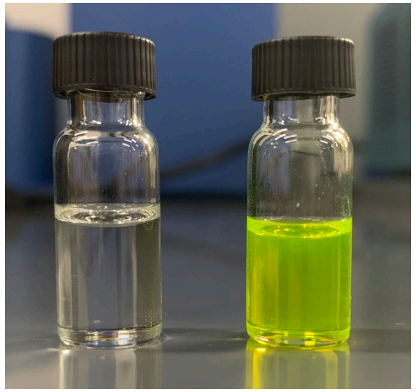
Photoswitchable fluorophore
e.g.: diarylethene BTFO



High energy electron transfers energy to solvent along its path

Solvent transfers energy to activate detector molecule





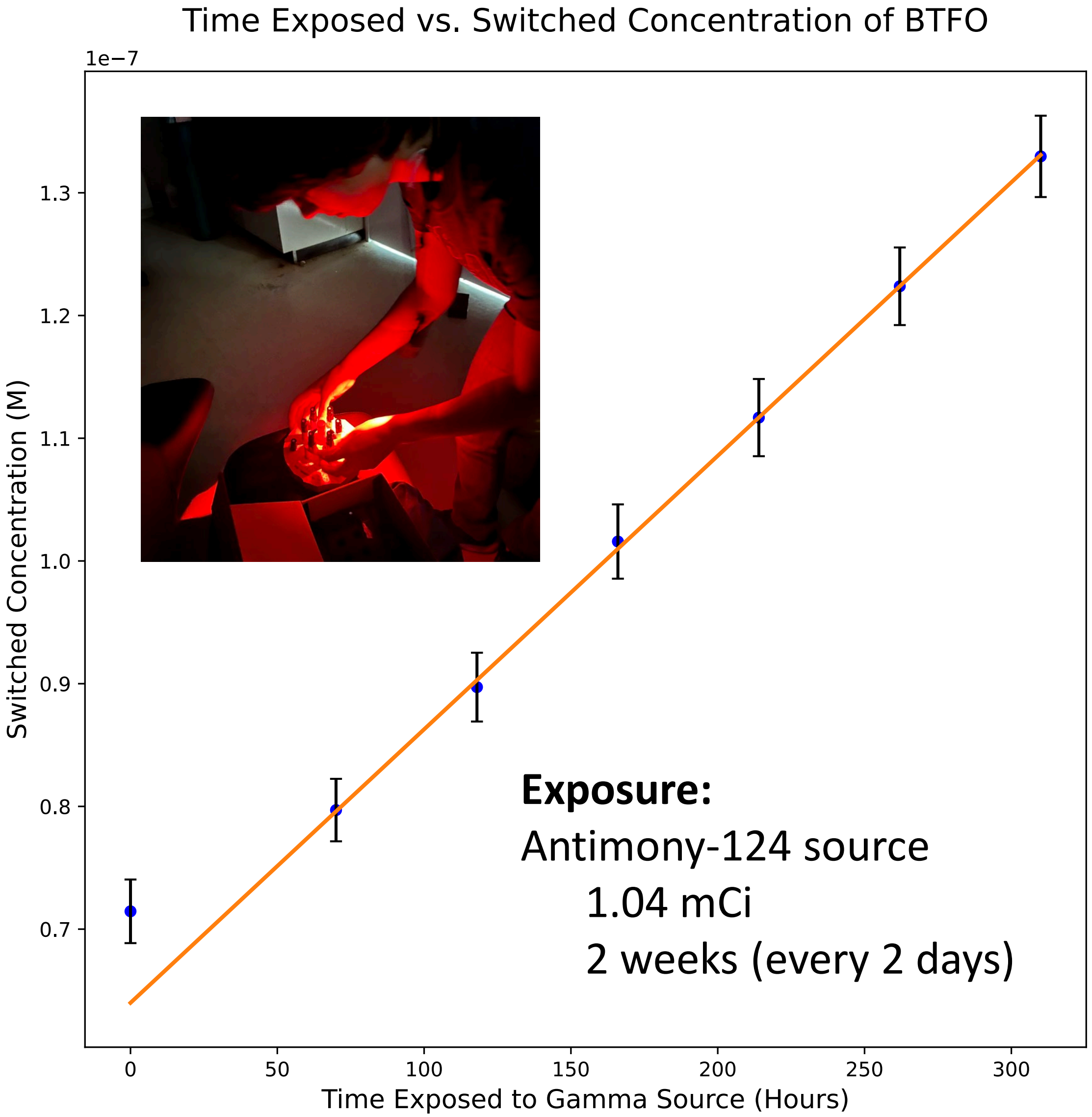
Typically, BTFO is switched to the 'on' state by direct absorption of UV light.

It can be switched 'off' with green light

1,2-Bis(2-methyl-6-phenyl-1-benzothiophen-1,1-dioxide-3-yl) perfluorocyclopentene (BTFO)

Shida JF, Spieglan E, Adams BW, Angelico E, Domurat-Sousa K, Elagin A, Frisch HJ, Squires AH. (2021) *Nucl. Inst. Meth. Phys. Res. A*

EXPERIMENT: BTFO is switched “ON” by recoil electrons from ~500 keV irradiation



Exposure:
Antimony-124 source
1.04 mCi
2 weeks (every 2 days)

(Rough) **Efficiency Bounding:**

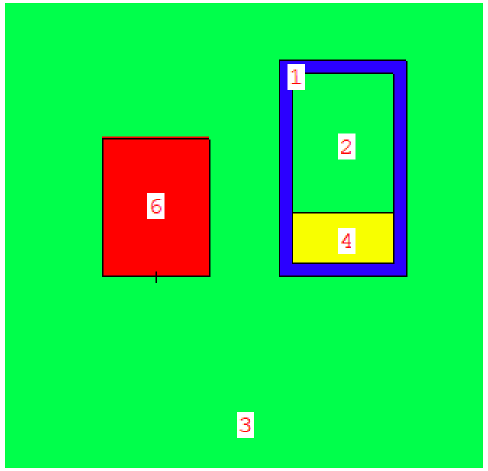
ΔC = +10^{-8} Molar per day
→ so ~10^{12} or 10^{13} molecules per day in ~1 ml

1 mCi = 3×10^{12} gamma photons (total) per day

MCNP Compton estimate:
~23 kHz, or 2×10^{9} per day interact with the sample

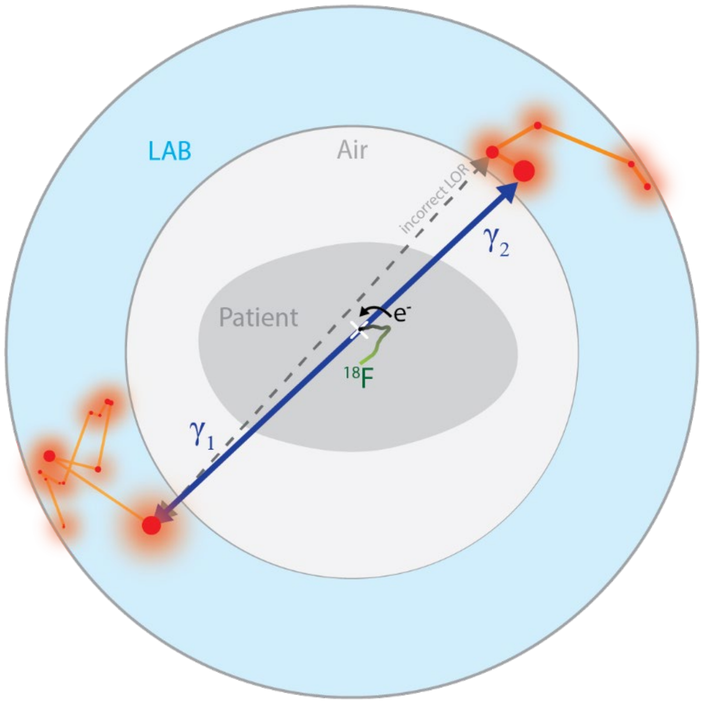
Need: >100 switching events per gamma photon

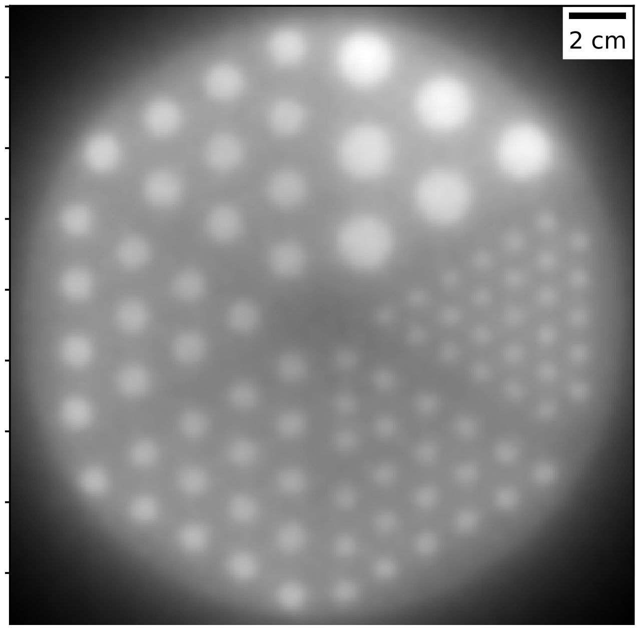
Get: 10^{3}-10^{4} switched molecules per Compton scatter
(< 1 keV/switch) ✓

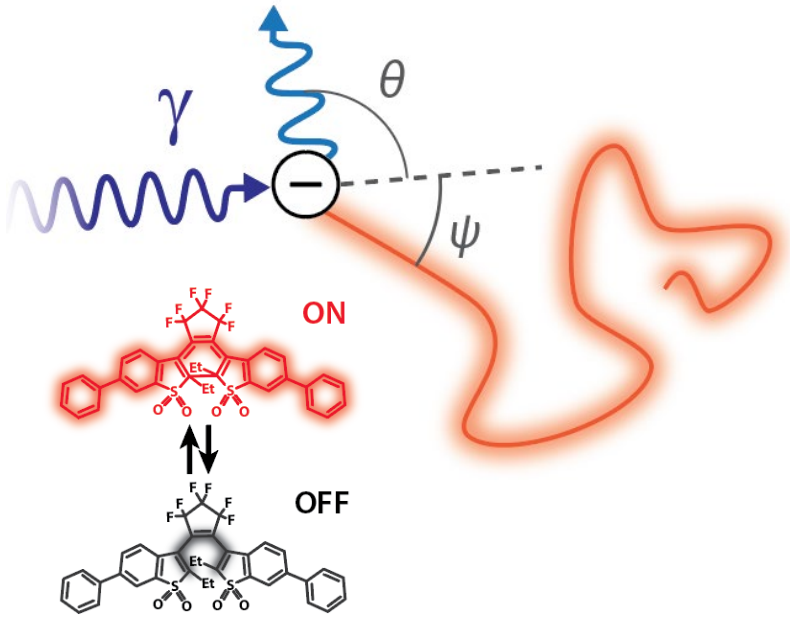


Dose estimation:
Monte Carlo N-Particle (MCNP) simulation

SUMMARY: Compton scattering in low-Z media shows promise for TOF-PET detection







Conclusions:

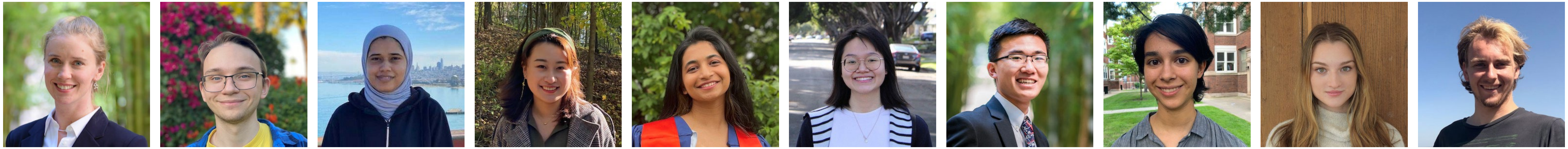
- Simulations show high sensitivity (70%) and resolution (2mm) for TOF-PET
- Reasonable baseline specs: 1 keV/switch, 0.5mm resolution
- BTFO (diarylethene) could be used as a reversible fluorescent marker

Next steps and future possibilities:

- Implement experimentally
- Incorporate Compton scattering geometry and timing information in ordering likelihood
- Modify for other applications

The Squires Group at the University of Chicago

SQUIRES LAB



Allison Squires | Andrés Cook, Physics | Ayesha Ejaz, Chemistry | Jiachong Chu, PME | Kavya Vaidya, PME | Dana Lin, PME undergrad | Kyle Lin, Biophysics + MD/PhD | Maya McDaniel, PME undergrad | Olivia Schaffer, PME undergrad | Trevor Anderberg, Physics

Postdoc and Ph.D. positions available!
E-mail asquires@uchicago.edu

Collaborators

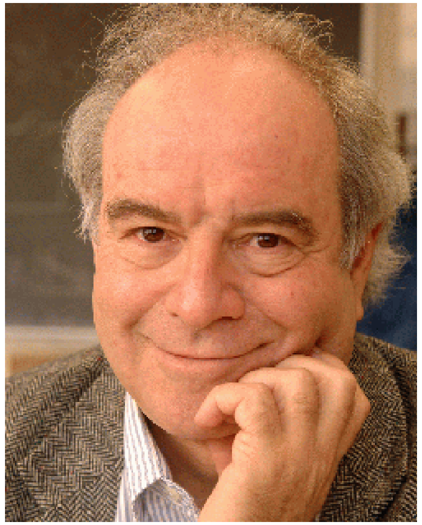
Prof. Henry Frisch (Physics)
Prof. Patrick La Riviere (Med)
Prof. Juan Collar (Physics)
Prof Allan Drummond (BMB)
Prof. David Pincus (MCGB)
Dr. Asif Ali (MCGB)
Prof. Andy Ferguson (PME)
Prof. Aaron Esser-Kahn (PME)
Dr. Justin Jureller (MRSEC)
Prof. Cheryl Kerfeld (MSU/LBNL)

NEUBAUER FAMILY
ASSISTANT PROFESSORS PROGRAM

THE UNIVERSITY OF CHICAGO
Chicago Materials Research Center

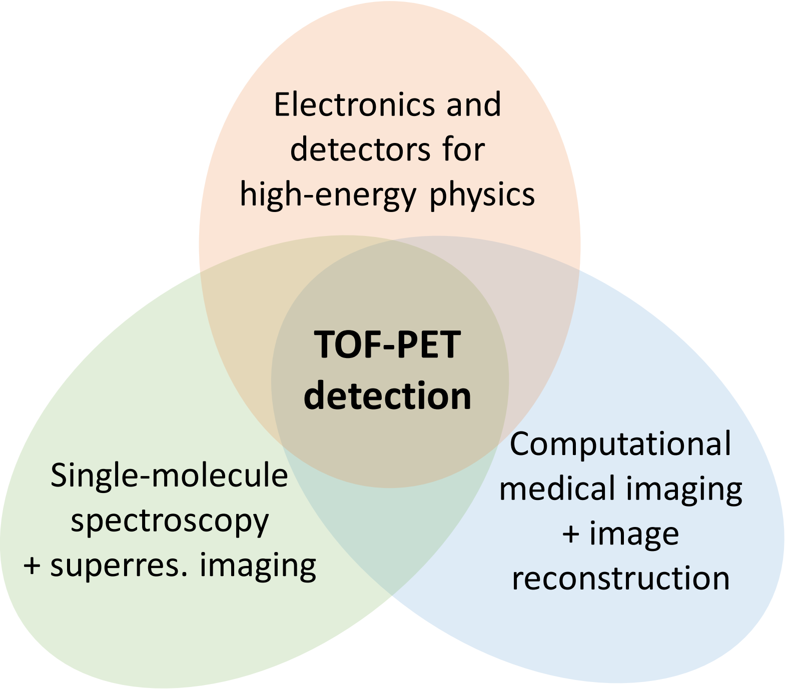
NSF
QuBBE
Award #2121044

ACKNOWLEDGEMENTS: Our cross-disciplinary team @ University of Chicago


Henry Frisch
Physics


Patrick La Riviere
Radiology

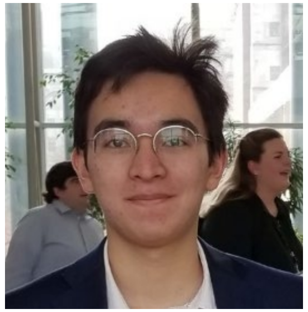

Allison Squires
Molecular Engineering



UNDERGRADUATES


Kepler Domurat-Sousa


Maya McDaniel


João Shida

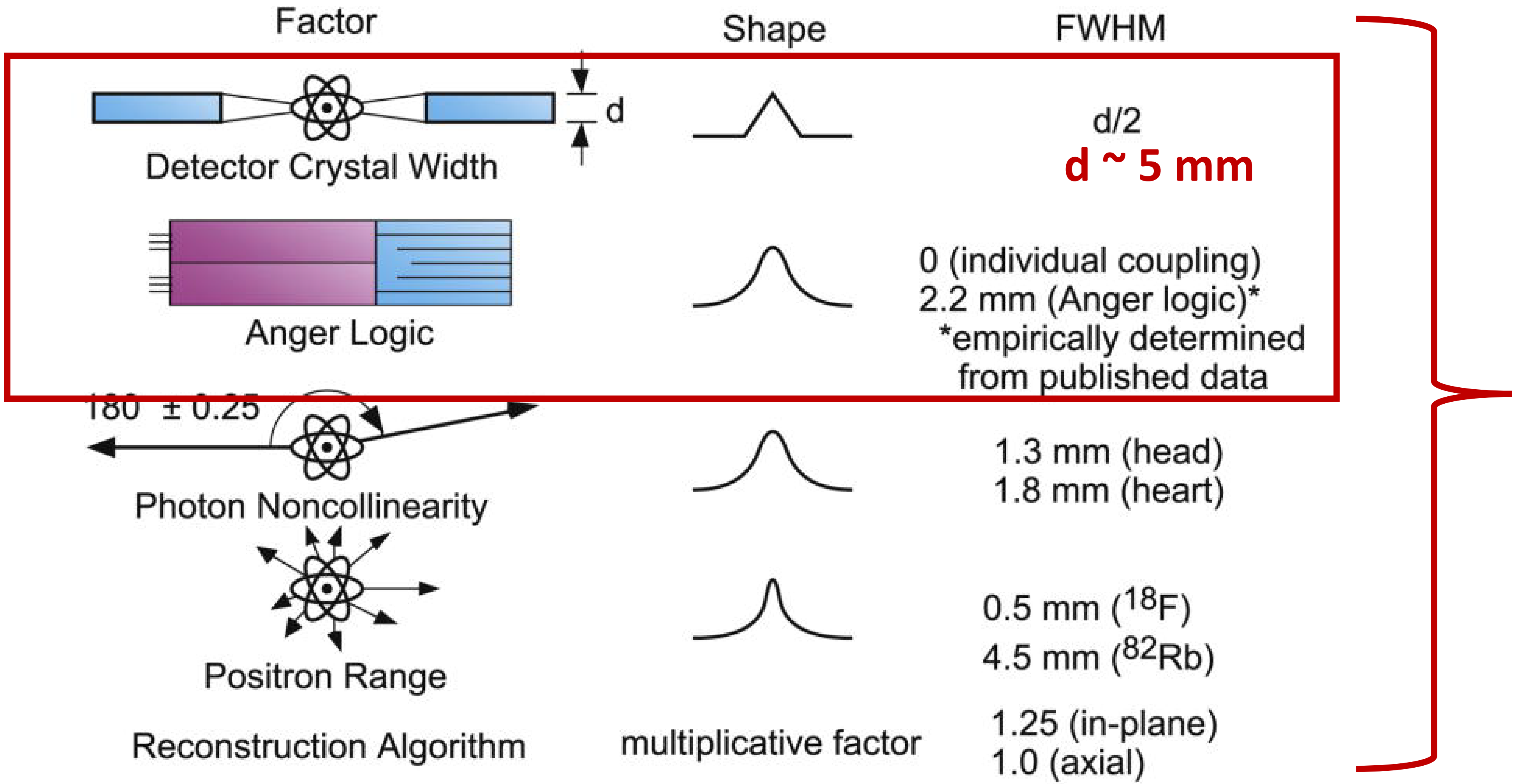

Eric Spieglan


Cameron Poe

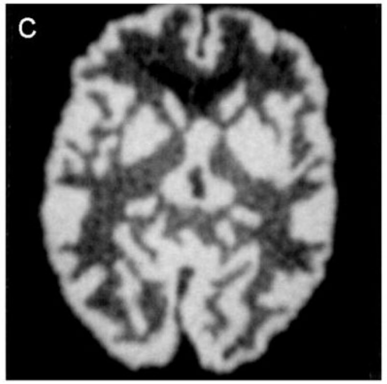
Special thanks:
Dr. Bernhard Adams
Prof. Juan Collar

Fermilab test beam
UChicago Med small animal irradiator

PROBLEM: PET Scan Resolution is Limited by Detector Size and Precision



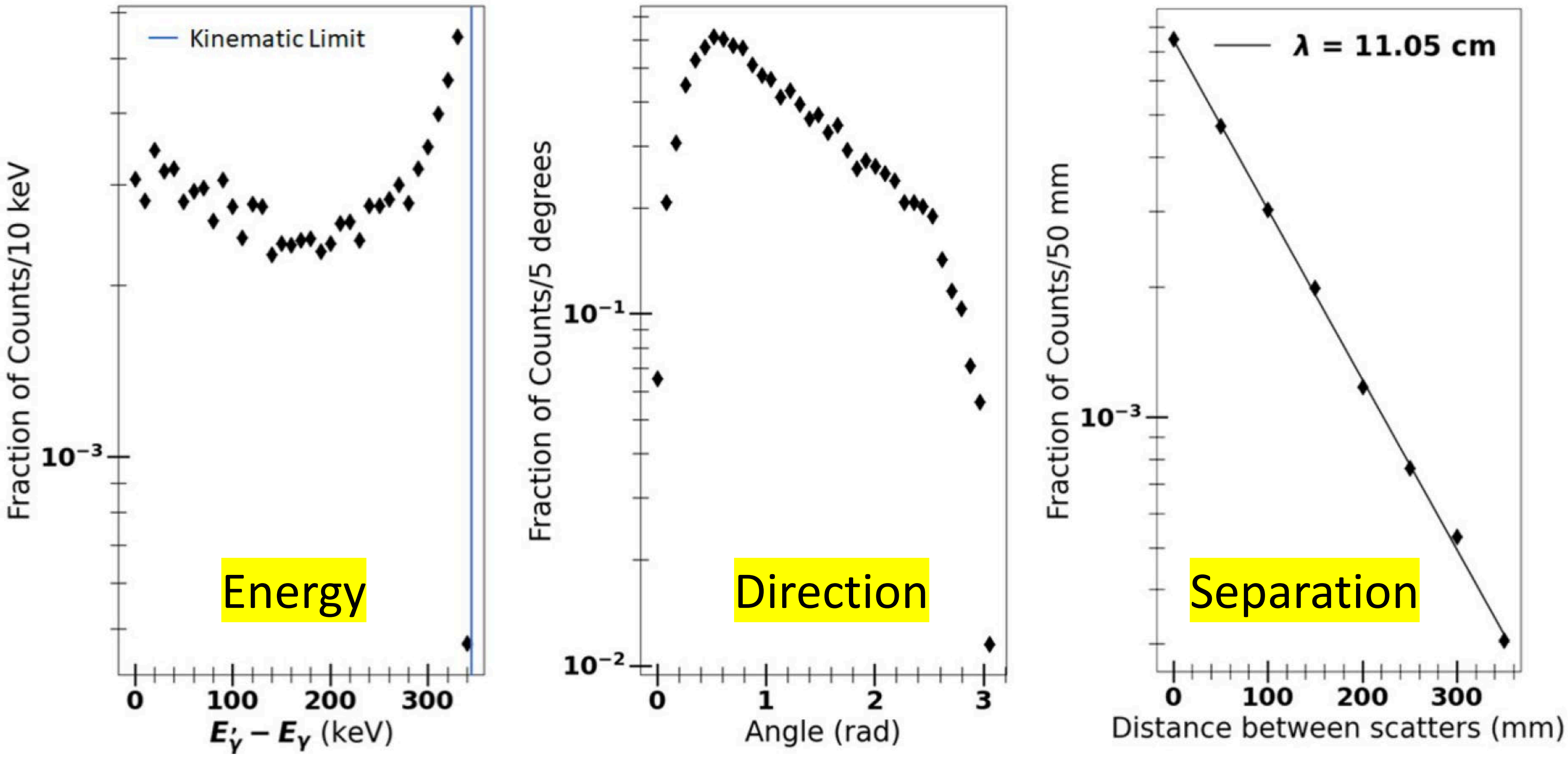
Few ~mm resolution at best



Moses, WW. (2011) “Fundamental Limits of Spatial Resolution in PET”. *Nucl. Instrum. Meth. Phys. Res. A*

SIMULATION: Expected energy, scattering direction, and spacing of recoil electrons

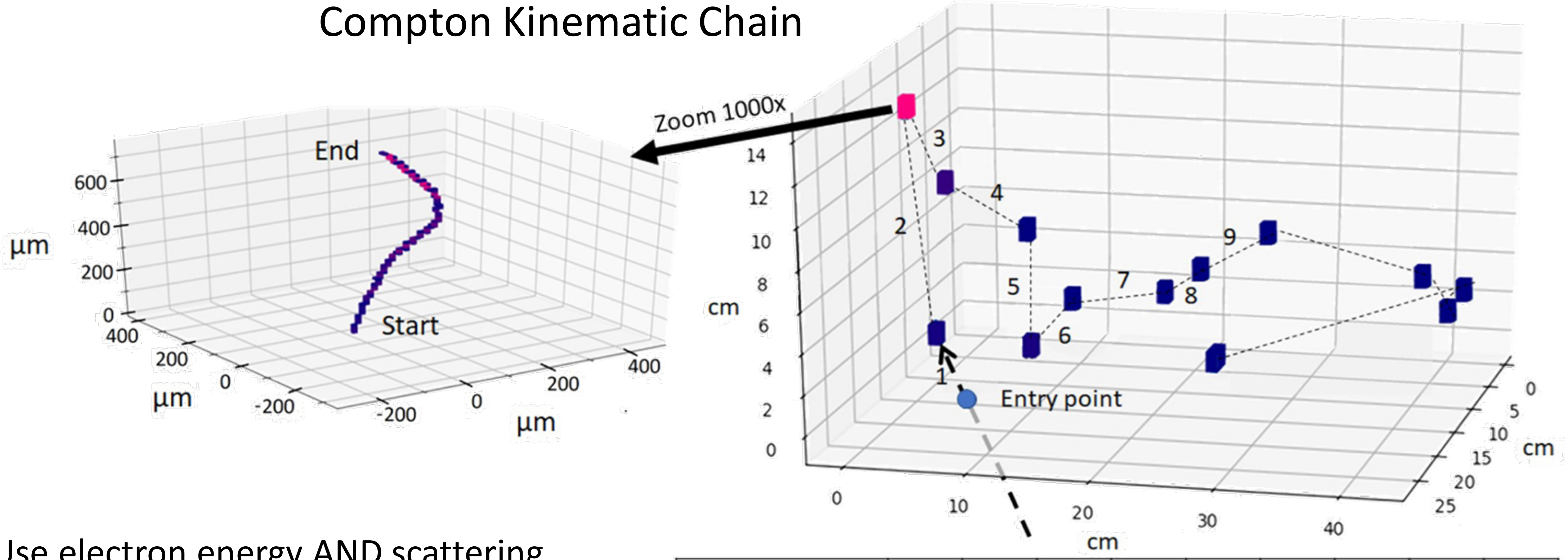
First recoil electron characteristics



Shida JF, Spieglan E, Adams BW, Angelico E, Domurat-Sousa K, Elagin A, Frisch HJ, Squires AH. (2021) *Nucl. Inst. Meth. Phys. Res. A*

SIMULATION: Disambiguate multiple scatters to determine original gamma trajectory

Compton Kinematic Chain



Segment Label	1	2	3	4	5	6	7	8	9
Energy (keV)	511	492	195	128	120	89	87	84	81

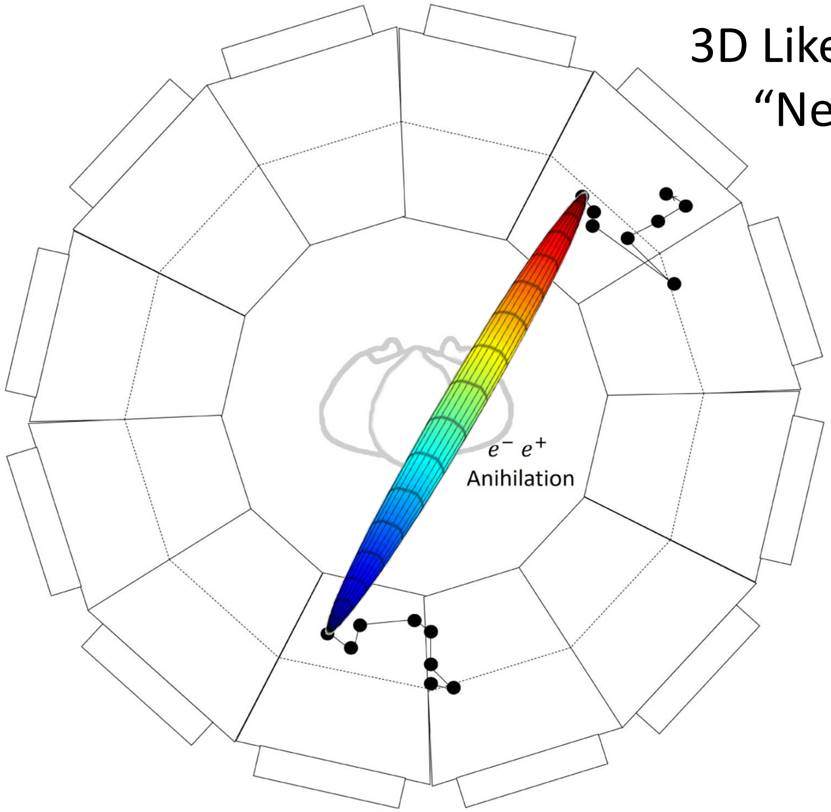
Use electron energy AND scattering direction to reconstruct kinematic chain

Ordering: ~90% accuracy (brightest 3)

Shida JF, Spieglan E, Adams BW, Angelico E, Domurat-Sousa K, Elagin A, Frisch HJ, Squires AH. (2021) *Nucl. Inst. Meth. Phys. Res. A*

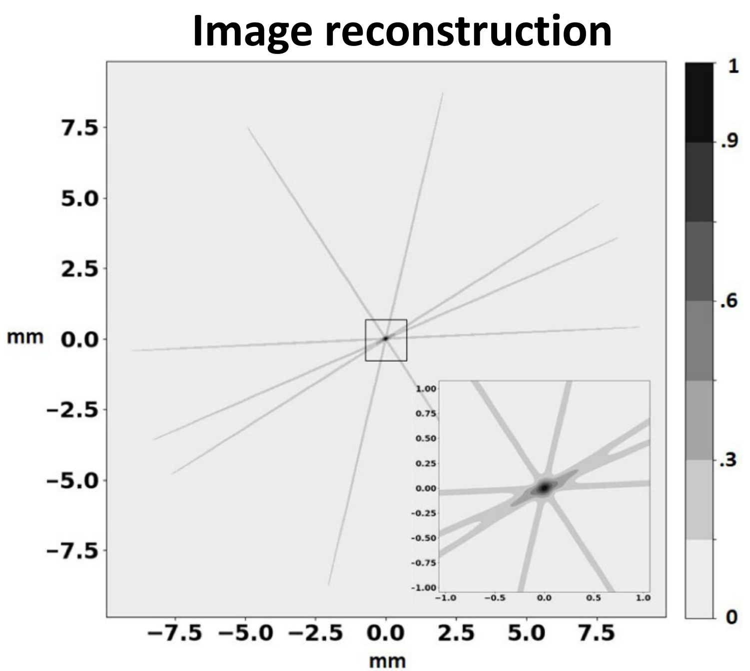
IMAGE RECONSTRUCTION: Use scattering sites to determine LOR for each gamma pair

3D Likelihood Gaussian
"Needle" Shaped



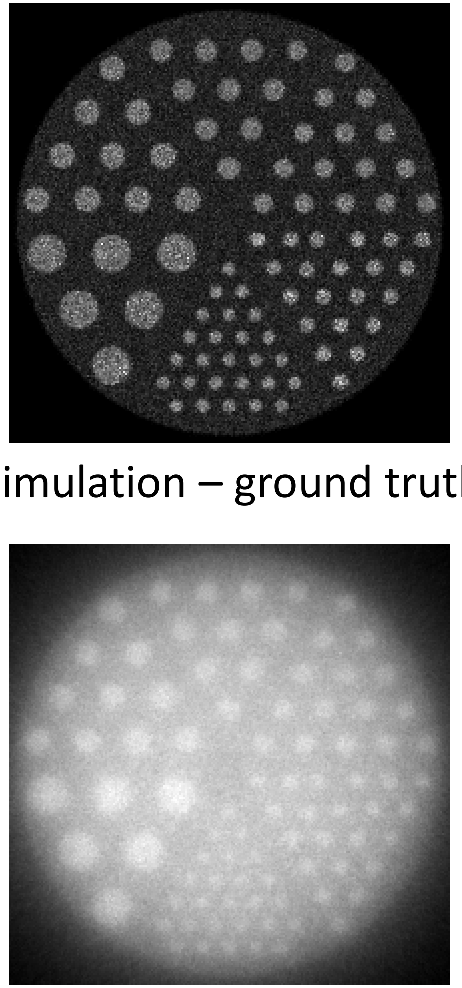
Uncertainty along the **axis**:
Tens of centimeters (timing)

Uncertainty **transverse** to axis:
Tens of microns (100x improvement)



Intersections of needles produce high image resolution due to transverse uncertainty improvement

1000x reduced dose simulation



Simulation – ground truth

Back-projection: S/N > 3

Shida JF, Spieglan E, Adams BW, Angelico E, Domurat-Sousa K, Elagin A, Frisch HJ, Squires AH. (2021) *Nucl. Inst. Meth. Phys. Res. A*

EXPERIMENT: Can BTFO be switched by gamma rays ~500 keV (similar to PET)?

Light-tight vials

2mL glass vial holding 0.4mL of solution

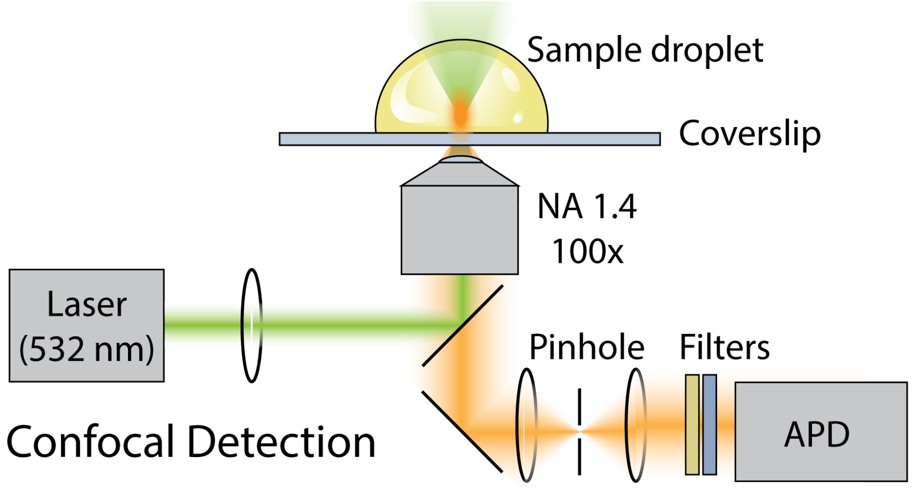
3D Printed Snaps to hold vials

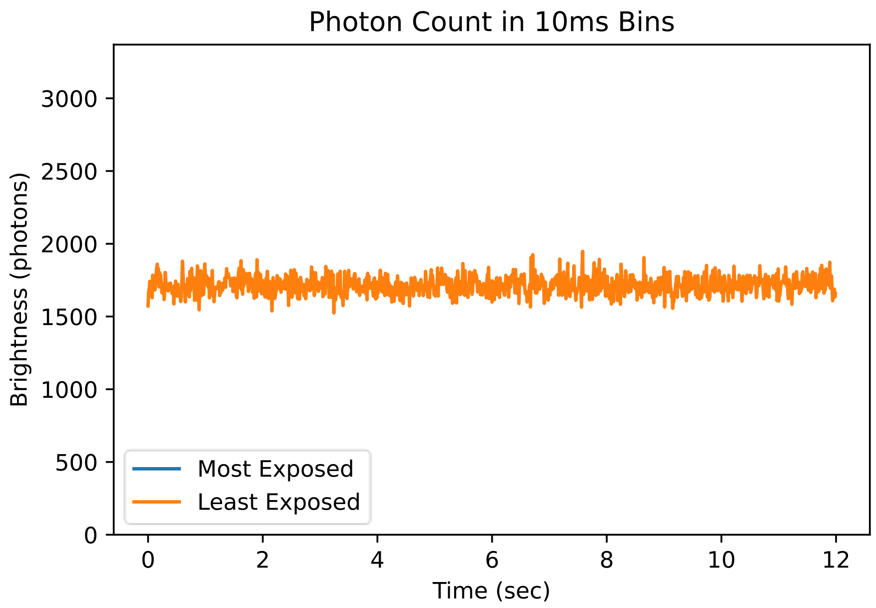
Sb-124 source holder

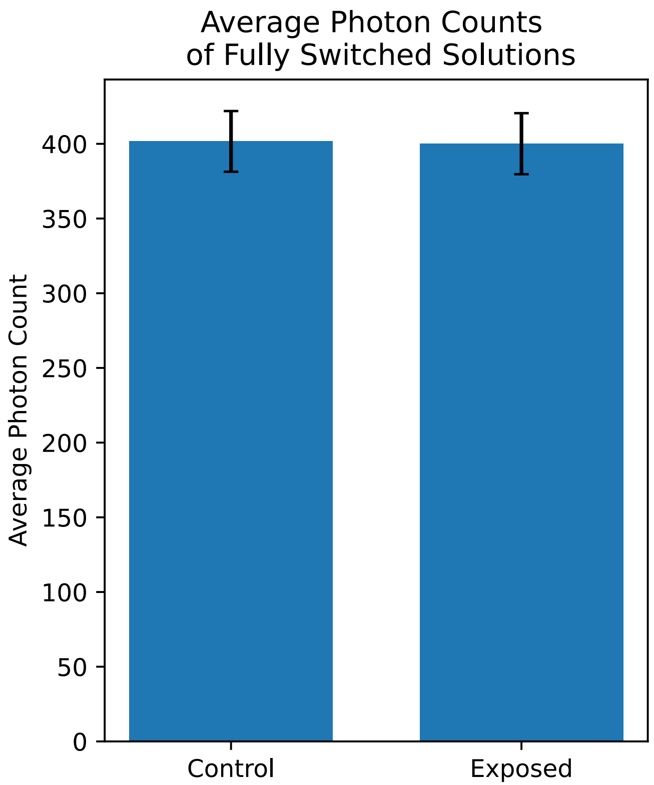
3D Printed Base

Exposure: Antimony-124 source
1.04 mCi
2 weeks (2 day time points)

MEASUREMENTS: Post-exposure confocal fluorescence (compared to control)

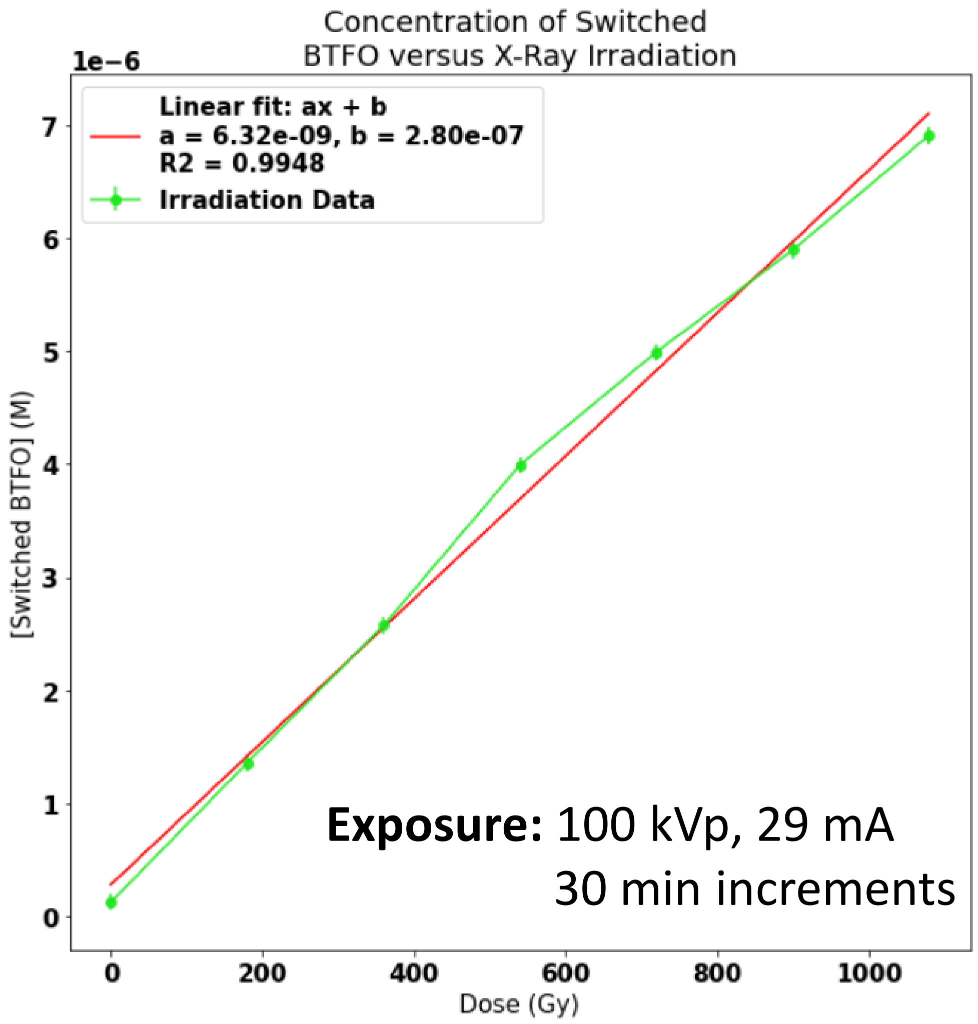


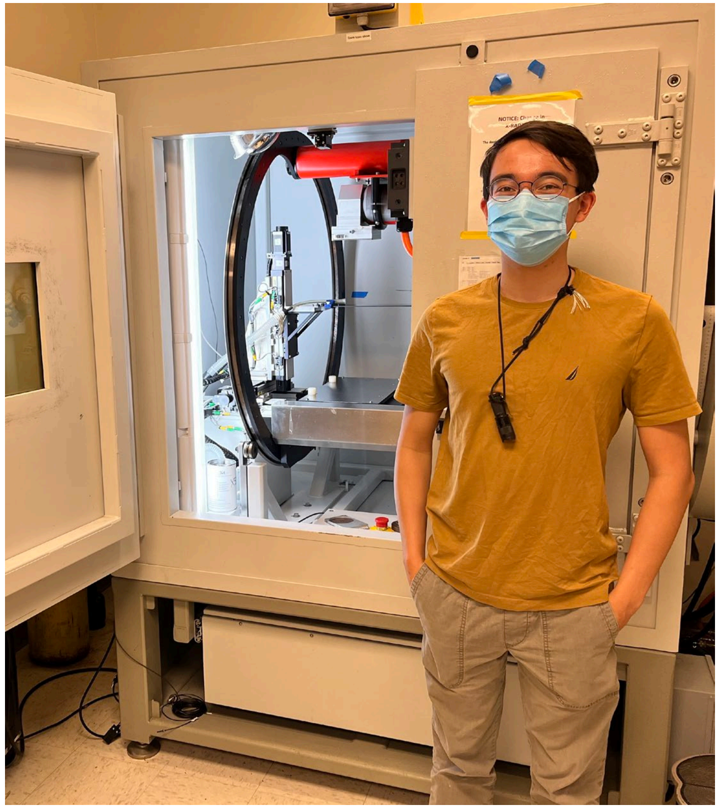




Exposure does not (measurably) inactivate or damage BTFO

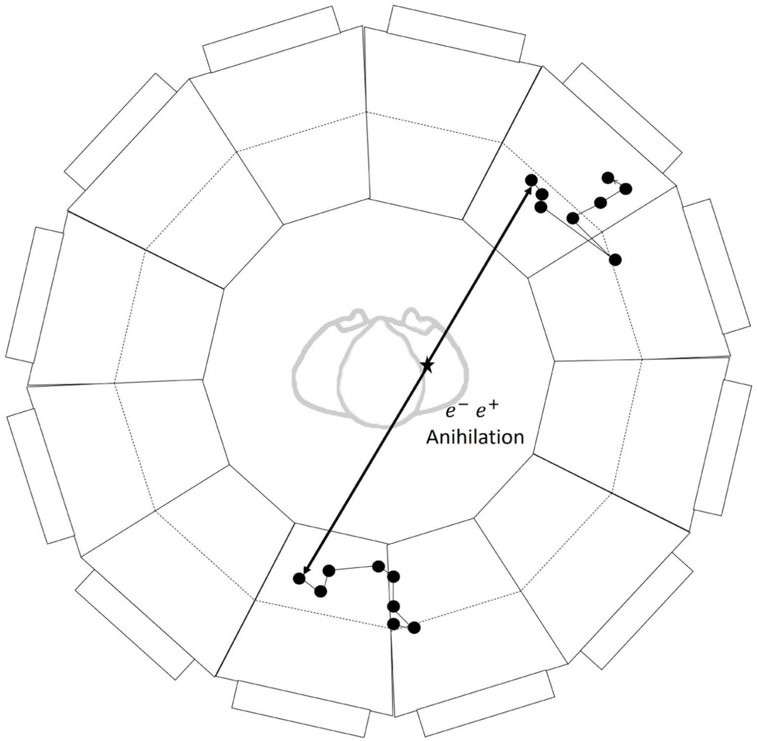
RESULTS: BTFO can also be switched to the fluorescent state by X-rays

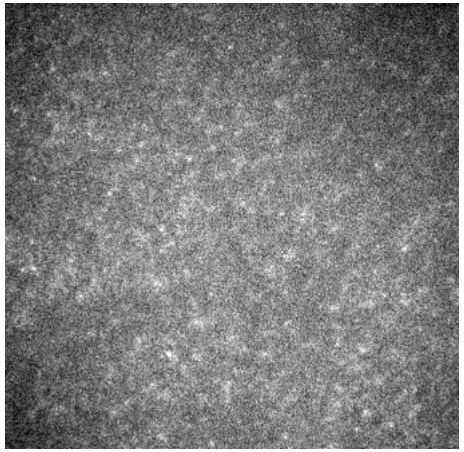




NEXT STEPS: Visualizing trails of Compton-scattered electrons

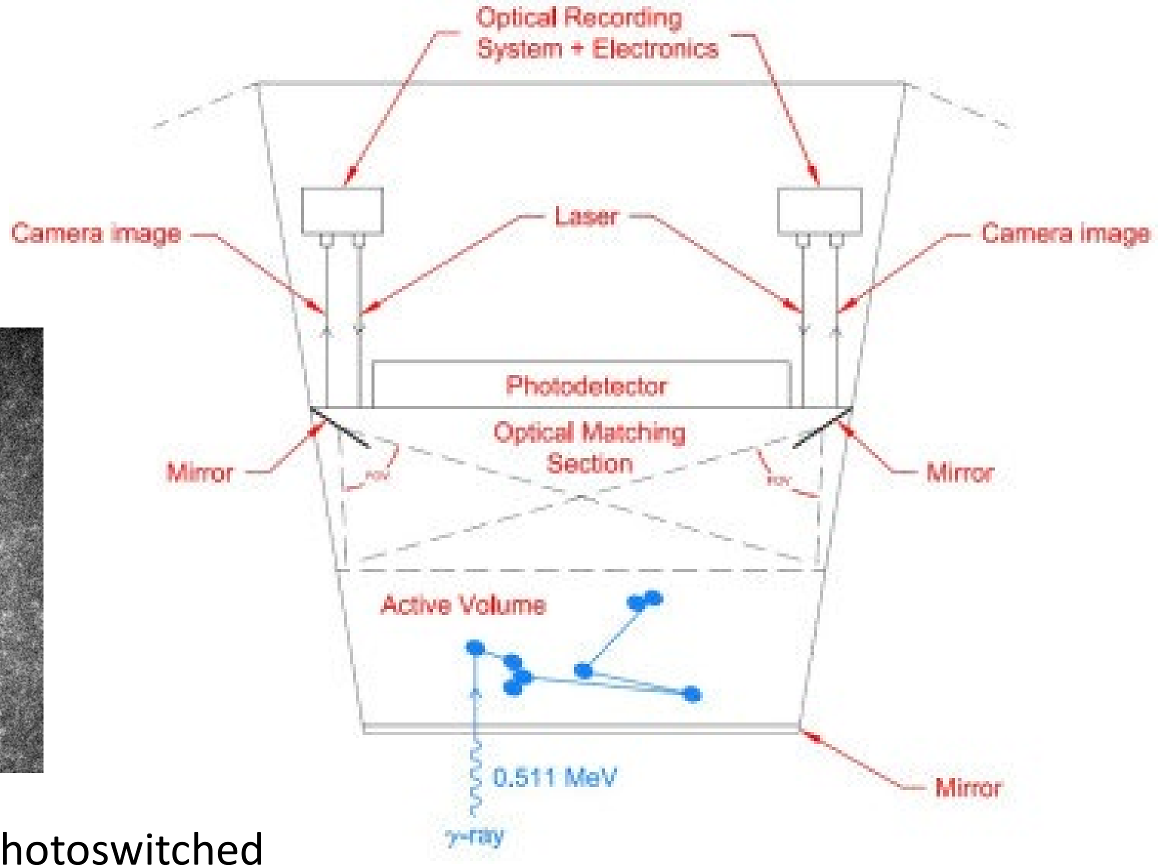
Future application: Improved PET detection by mapping Compton scatter kinematic chain



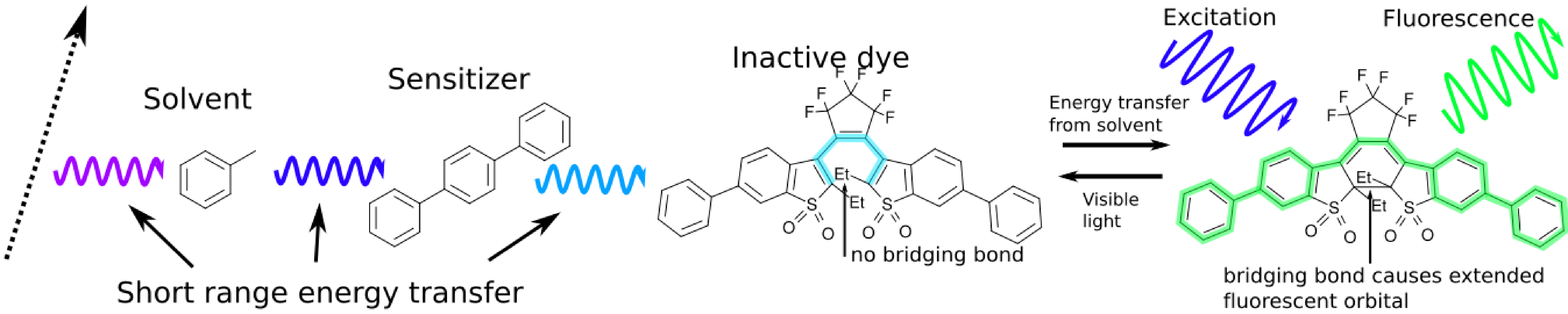


Imaging: single BTFO in LAB → photoswitched

Optical recording: Scanned imaging + reset system



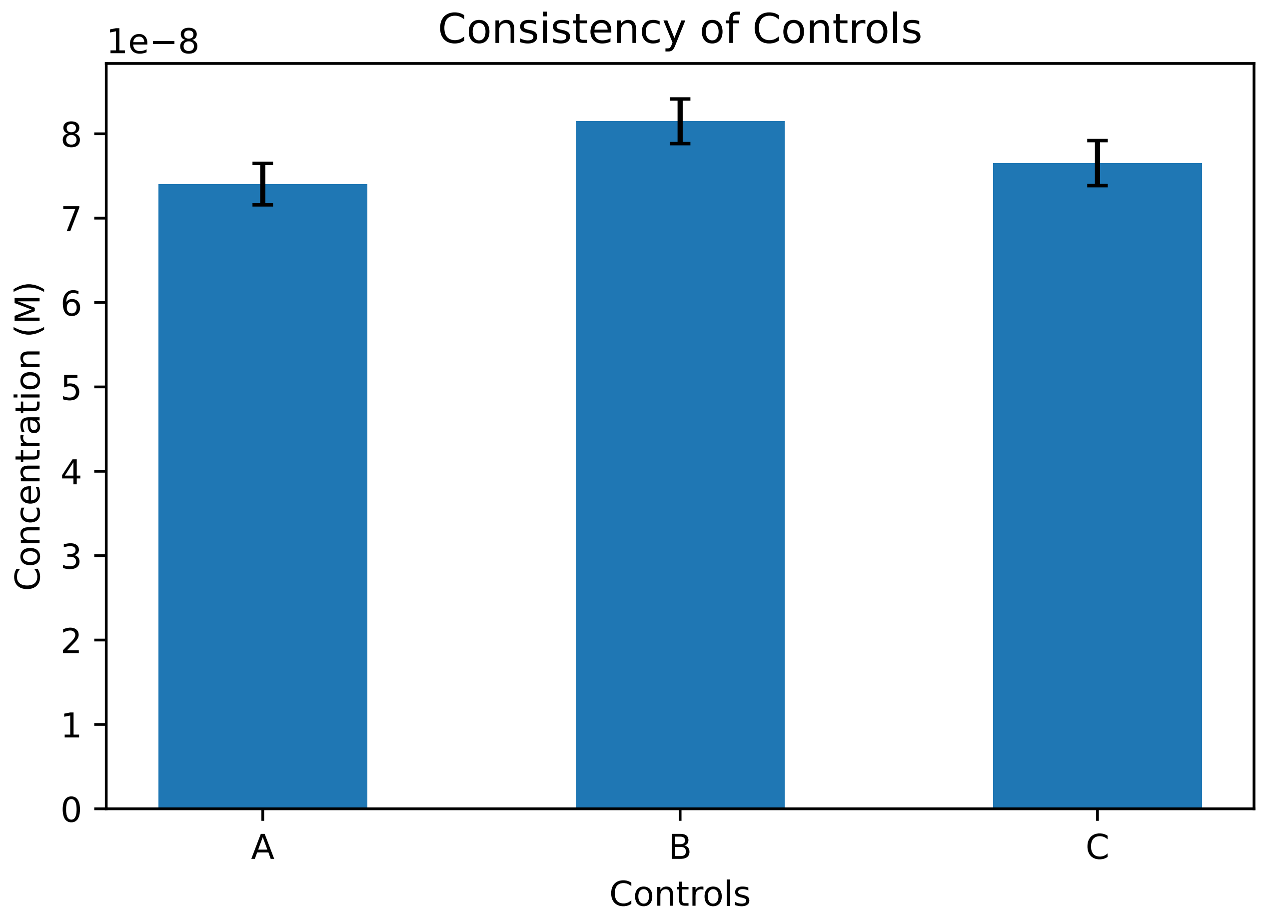
Generalizability



Visualize any process that deposits energy spatially in the solvent

E.g. Double-beta decay;
X-rays;
Y-rays;

Controls



Control A: Stored in foam in the light-proof box with the rest of the samples.
Control B: Wrapped in cinefoil in the light-proof box with the rest of the samples.
Control C: Wrapped in cinefoil and stored in a dark cabinet, untouched for the duration of the experiment.

ASSUMPIONS: Switchillator simulations

	Parameter	Symbol	Value	Comment
Scintillator Properties				
1	Scintillation Yield	Y_{scint}	$> 2 \times 10^3$	# of scintillation photons per MeV
2	Scintillation Rise Time	τ_r	TBD	1/e rise time of scintillation light
3	Scintillation Decay Time	τ_d	TBD	1/e decay time of scintillation light
Switchillator Properties				
1	Activation Yield	Y_{act}	$> 5 \times 10^3$	# of ON fluorophores per MeV deposited
2	Activation Wavelength	λ_{act}	< 400 nm	Peak inactive to active wavelength
3	Excitation Wavelength	λ_{ex}	350-650 nm	At max separation
4	Dye Ratio	Z_{dye}	$< 10^{-12}$	Ratio of rates of background activation to fluorescence at λ_{ex}
5	On-State Lifetime	τ_{ON}	3×10^{-7}–10^{-1} s	1/e Lifetime of ON fluorophores
6	Fluorescence brightness	$\varepsilon \cdot \Phi_{fl}$	$>10^3$/(M cm)	Rate of emission from active dye
7	Mean Absorption Length	$\chi(\lambda_{ex})$	> 6 m	1/e absorption length at λ_{ex}
8	Emission Wavelength	λ_{fl}	400-700 nm	Wavelength of fluorescence light
9	# of photons per activated fluorophore	N_{fl}	> 500	Mean # of fluorescent photons extracted per fluorophore before deactivation

Shida JF, Spieglan E, Adams BW, Angelico E, Domurat-Sousa K, Elagin A, Frisch HJ, Squires AH. (2021) *Nucl. Inst. Meth. Phys. Res. A*