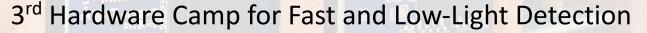
PET as an MPPC (SiPM) Application: Time-of-Flight PET for Proton Therapy

John Cesar On behalf of the TPPT Consortium March 9th, 2024





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E ZLOL



Outline:

- Our background
- PET imaging
- SiPMs in PET
- The TPPT project
- Future Ideas

Our Background

From particle physics to medical physics...(but also still involved in particle physics)

Our Background: The UT Lang Group

• Historically, our group has been conducting research in high energy physics

SSC (Superconducting Super Collider, cancelled in 1993)

 $\,\circ\,$ Rare $\rm K_L\, decays$

 $\circ~$ Neutrino oscillations

- \circ Search for neutrinoless double beta decay
- $\,\circ\,$ Search for coherent neutrino interactions at a reactor
- \odot We have participated in all main aspects of these particle physics endeavors

 $\,\circ\,$ designed, fabricated, deployed new instrumentation

 $\,\circ\,$ developed physics analysis software

 \odot Funded by (over the years)

 $\circ~$ U. of Texas

o DOE

 \circ NSF

 \circ Fermilab

o URA

○ CNRS (France)

 $\,\circ\,$ We have always had interests in contributing to medical physics

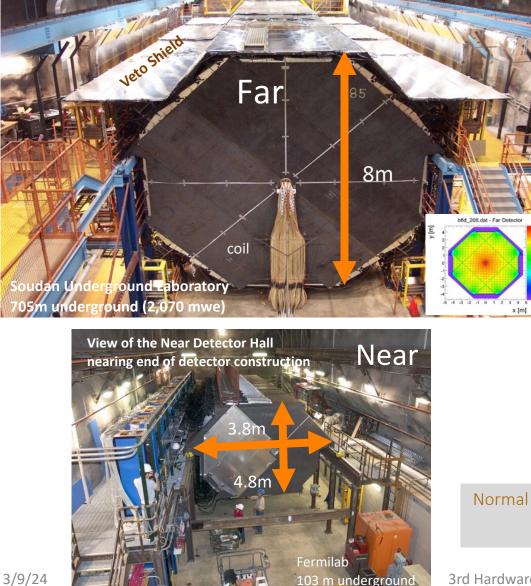
 $\,\circ\,$ Turns out that medical imaging is an exciting field to contribute to!



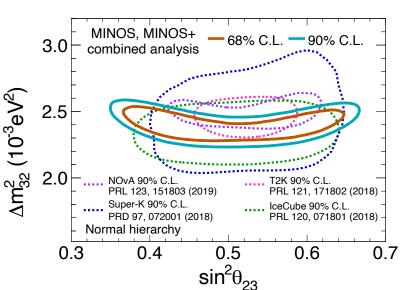


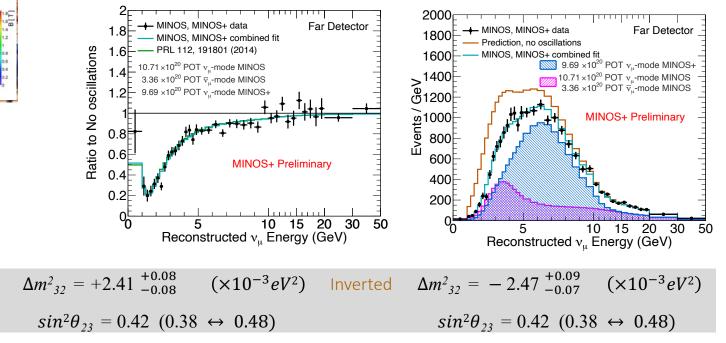


Our Background: MINOS/MINOS+

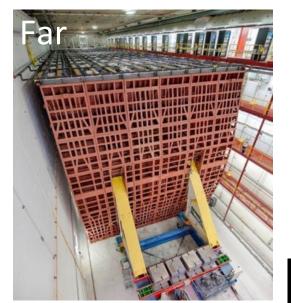


- Large-scale, long baseline neutrino oscillations experiment
- Operated 2005 2016
- Precision measurements of mixing parameters



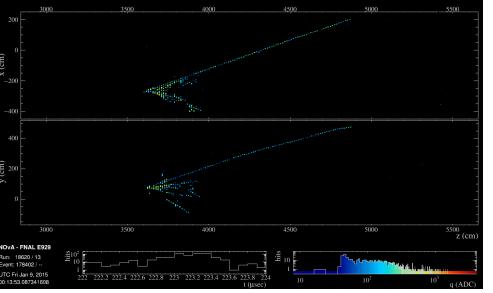


Our Background: NOvA



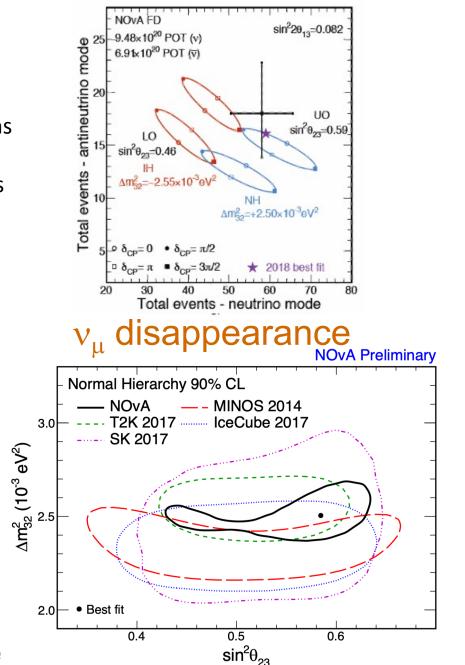


- Successor to MINOS
- Large-scale, long base-line neutrino oscillations experiment
- Precision measurements of mixing parameters
- Potential mass hierarchy resolution
- Still in operation



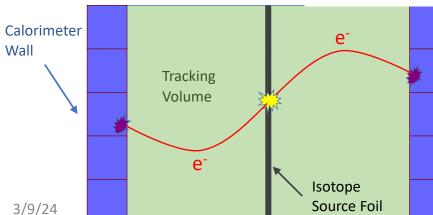
3rd Hardware Camp for Fast and Low-Light Dete

v_e appearance



Our Background: NEMO-3/SuperNEMO





ASECTOR

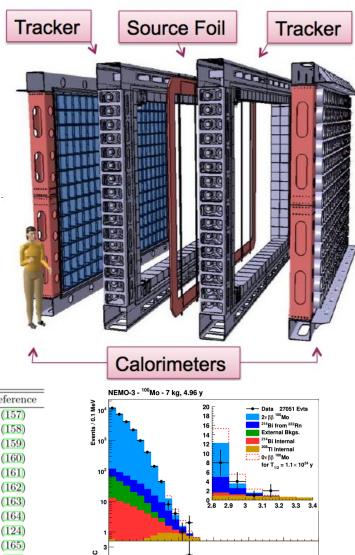
В

mode (6180 cells)

- Neutrinoless double-beta decay search experiment
- Novel multi-observable multiisotope approach
- NEMO-3 operated from 2003 -2011
- SuperNEMO demonstrator module currently being commissioned

Isotope	$T_{1/2}^{0\nu}$ (×10 ²⁵ y)	$\langle m_{\beta\beta} \rangle ~(\mathrm{eV})$	Experiment	Reference
^{48}Ca	$> 5.8 \times 10^{-3}$	< 3.5 - 22	ELEGANT-IV	(157)
76 Ge	> 8.0	< 0.12 - 0.26	GERDA	(158)
	> 1.9	< 0.24 - 0.52	MAJORANA DEMONSTRATOR	(159)
82 Se	$> 3.6 \times 10^{-2}$	< 0.89 - 2.43	NEMO-3	(160)
96 Zr	$> 9.2 \times 10^{-4}$	< 7.2 - 19.5	NEMO-3	(161)
^{100}Mo	$> 1.1 \times 10^{-1}$	< 0.33 - 0.62	NEMO-3	(162)
^{116}Cd	$> 1.0\times 10^{-2}$	< 1.4 - 2.5	NEMO-3	(163)
128 Te	$> 1.1 \times 10^{-2}$	_		(164)
130 Te	> 1.5	< 0.11 - 0.52	CUORE	(124)
136 Xe	> 10.7	< 0.061 - 0.165	KamLAND-Zen	(165)
	> 1.8	< 0.15 - 0.40	EXO-200	(166)
150 Nd	$> 2.0 \times 10^{-3}$	< 1.6 - 5.3	NEMO-3	(167)

3rd Hardware Camp for Fast and Low-Light Detection



PET Imaging

PET = Positron Emission Tomography and it is a subset of the larger medical imaging field...

PET Imaging: A Subset of Medical Imaging





MRI (Magnetic Resonance Imaging)

PET (Positron Emission Tomography)

And there are others:

- SPECT imaging
- X-ray imaging
- Ultrasound imaging
- ...



PET and SPECT are <u>nuclear</u> medical imaging techniques

- Radiation being used/detected is internal rather than external
- Employ radiopharmaceuticals
- Emphasis on imaging <u>function</u> (metabolism, etc.) not <u>structure</u> (anatomy)

PET Imaging: A Subset of Medical Imaging



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PET Imaging: Positron Emission

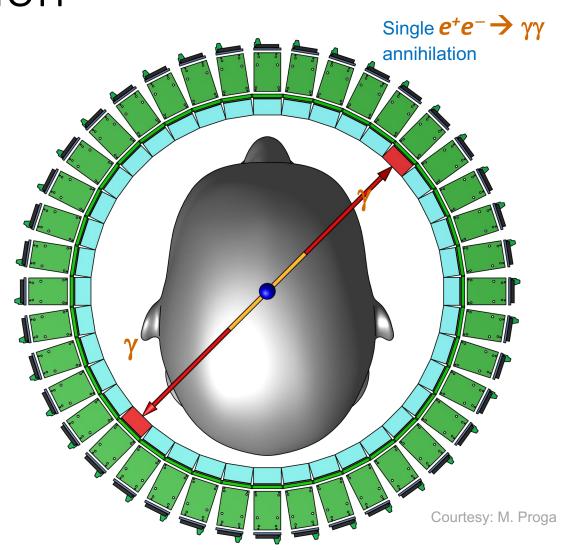
Injection of ¹⁸F-fluorodeoxyglucose (¹⁸FDG) or other suitable radiopharmaceuticals

$$^{18}\text{F} \rightarrow ^{18}\text{O} + e^+ + v_e$$

$$e^+ + e^- \rightarrow \gamma + \gamma$$

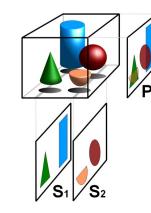
 $E = mc^2$

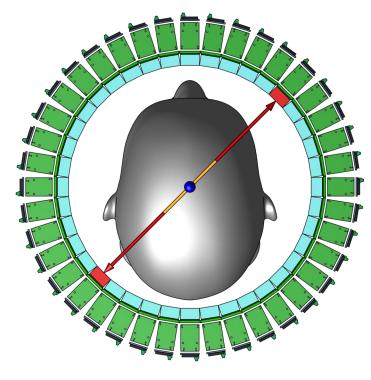
mass of the electron = $511 \ keV$ mass of the electron = mass of the positron $E_{\gamma} = 511 \ keV$



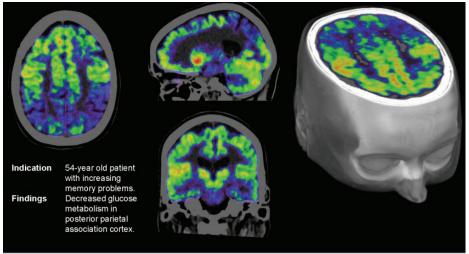
LOR = line of response = the line formed by the trajectories of the two back-to-back gammas

PET Imaging: Tomography





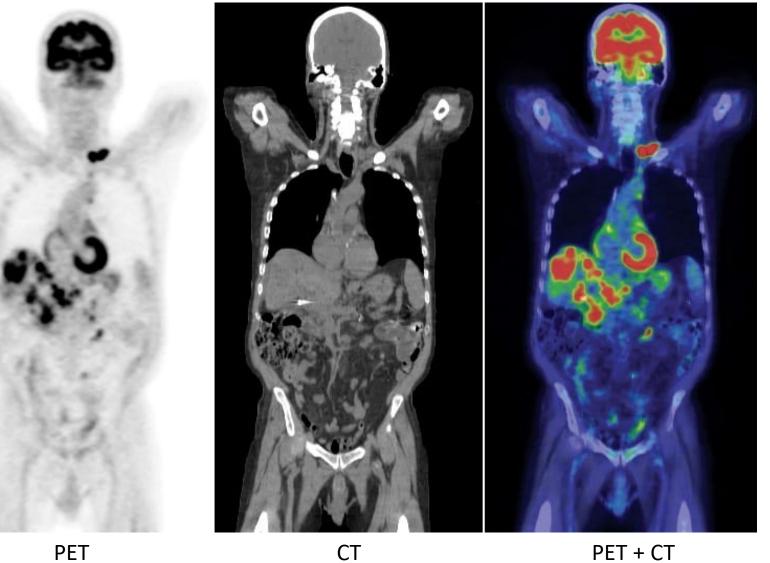
One LOR is not enough, the annihilation could have occurred anywhere along the LOR With many LORs from the same region, their intersections can be traced back to a common source



Source: Data Courtesy of Medical Imaging Center, Grand Rapids, MI, USA, Dr. P. Shreve

Doing this along different planes then allows for full 3D image reconstruction of activity and/or structure (CT is also tomographic)

PET Imaging: Conventional PET + CT



Recall...

CT = structural PET = functional

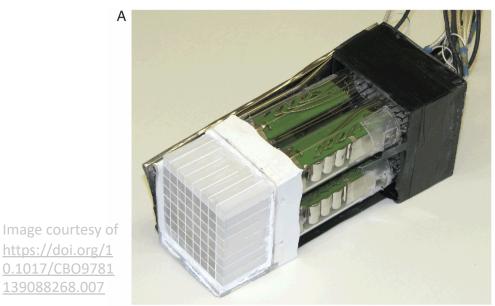
3rd Hardware Camp for Fast and Low-Light Detection

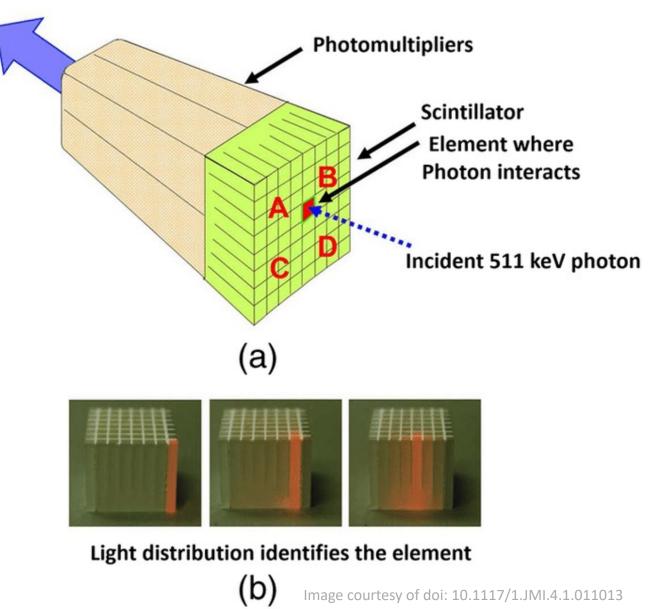
SiPMs in PET

Modern PET scanner technology

SiPMs in PET: Early PMT-based Scanners

- Need to detect and localize emitted gammas •
 - Space \rightarrow gives us LORs •
 - Time \rightarrow Define coincidences •
 - Avoid randoms
 - Maybe do more...
- Early scanners used scintillators + PMTs
- But PMTs often had larger surface areas than ideal ٠
 - Needed more pixelization •
 - Early designs had to be clever... •





https://doi.org/1

SiPMs in PET: Comparisons

	PD	APD	MPPC	PMT
Gain	1	10 ²	to 10 ⁶	to 10 ⁷
Quantum efficiency	Highest	High	Medium	Low
Operation voltage	5 V	100 to 500 V	30 to 60 V	800 to 1000 V
Large area	No	No	Medium	yes
Multi channel with narrow gap	Yes	Yes	Yes	No
Readout circuit	Complex	Complex	Simple	Simple
Noise	Low	Middle	Middle	Low
Uniformity	Excellent	Good	Excellent	Good
Energy resolution	High	Medium	High	High
Temperature sensitivity	Low	High	Medium	Low
Ambient light immunity	Yes	Yes	Yes	No
Magnetic resist	Yes	Yes	Yes	No
Compact & Weight	Yes	Yes	Yes	No

Image courtesy of https://www.hamamatsu.com/eu/en/product/optical-sensors/mppc/what_is_mppc.html

SiPMs in PET: Comparisons

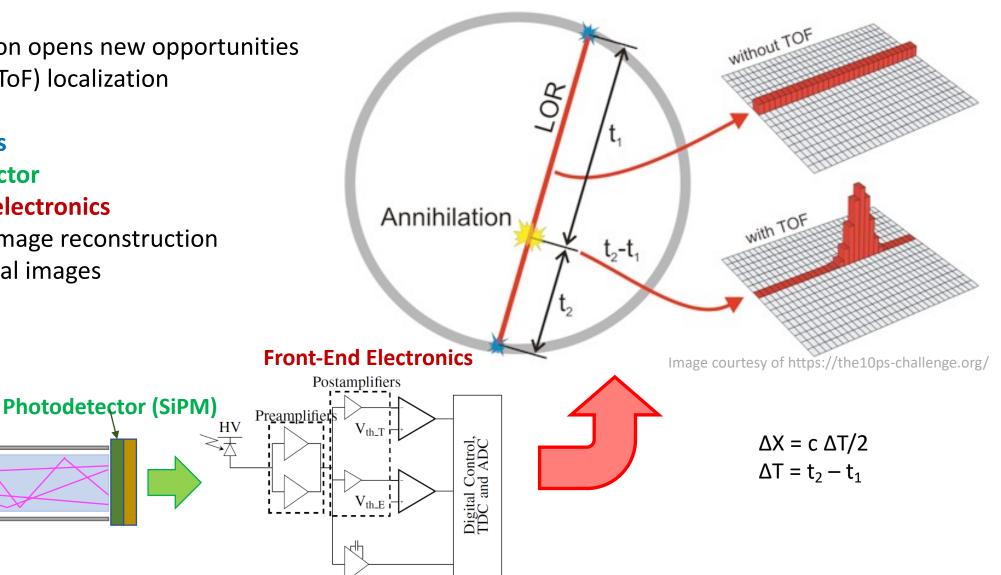
	PD	APD	MPPC	PMT	
Gain	1	10 ²	to 10 ⁶	to 10 ⁷	Comparable gain to PMTs
Quantum efficiency	Highest	High	Medium	Low	and better QE
Operation voltage	5 V	100 to 500 V	30 to 60 V	800 to 1000 V	
Large area	No	No	Medium	yes	
Multi channel with narrow gap	Yes	Yes	Yes	No	Good for better pixelization (spatial
Readout circuit	Complex	Complex	Simple	Simple	position resolution) and less dead space!
Noise	Low	Middle	Middle	Low	
Uniformity	Excellent	Good	Excellent	Good	
Energy resolution	High	Medium	High	High	Allows for combined PET
Temperature sensitivity	Low	High	Medium	Low	+ MR (function + structure imaging)
Ambient light immunity	Yes	Yes	Yes	No	
Magnetic resist	Yes	Yes	Yes	No	Compactness also open
Compact & Weight	Yes	Yes	Yes	No	new opportunities for PET

Image courtesy of https://www.hamamatsu.com/eu/en/product/optical-sensors/mppc/what_is_mppc.html

SiPMs in PET: Fast Timing

- Fast gamma detection opens new opportunities
 - Time-of-Flight (ToF) localization
- Three ingredients:
 - Fast scintillators
 - Fast photodetector
 - Fast front-end electronics
- Leads to improved image reconstruction
 - Less noise in final images

Reflector

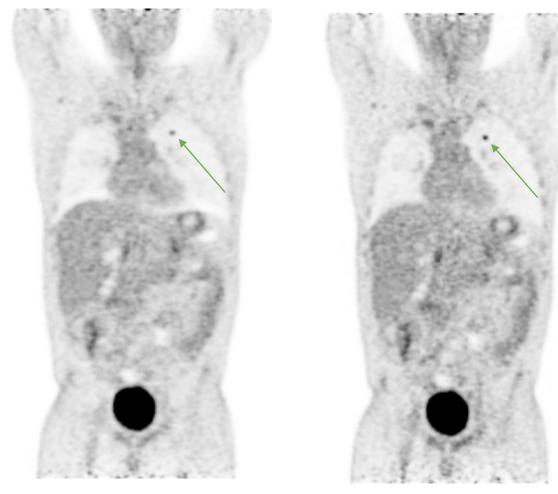


Scintillator

SiPMs in PET: Time-of-Flight PET

Non-TOF

3 minute/bed injection of ¹⁸Ffluorodeoxyglu cose (¹⁸FDG)



Borrowed from Dr. Maurizio Conti Director, PET Physics and Reconstruction Siemens Medical Solution USA, Inc, Knoxville, TN, USA

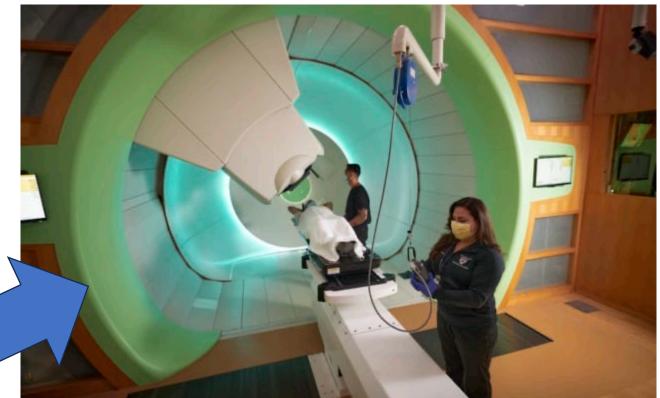


TOF (550 ps)

SiPMs in PET: Compact Size

- Compactness of SiPMs also present new opportunities
 - Double-ended readout (to be discussed later)
 - In-beam PET imaging
 - Can be used with proton therapy
 - Which leads us to





SiPMs in PET: Compact Size

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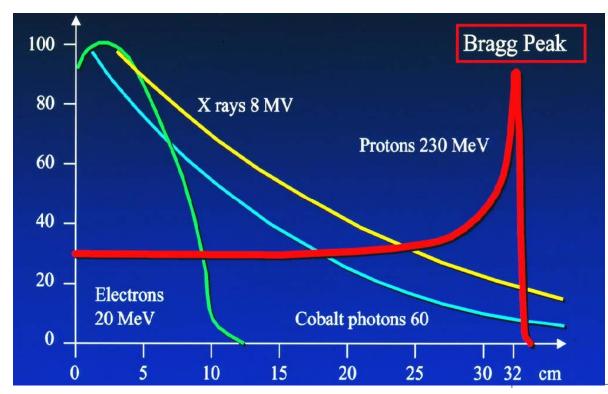
Current conventional PET/CT scanners too large for this because imaging (diagnostics) and treatment (therapy) don't mix...yet

The TPPT Project

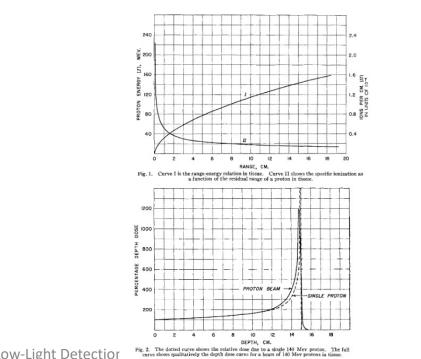
Time-of-Flight PET for Proton Therapy: PET feedback to provide imageguidance during proton therapy

The TPPT Project: Proton Therapy History

"The proton proceeds through the tissue in very nearly a straight line, and the tissue is ionized at the expense of the energy of the proton until the proton is stopped. [the] dose is many times less where the proton enters the tissue at high energy than it is in the last centimeter of the path where the ion is brought to rest. [...][in a] strictly localized region within the body, with but little skin dose. It will be easy to produce well collimated narrow beams of fast protons, and since the range of the beam is easily controllable, precision exposure of well defined small volumes within the body will soon be feasible."



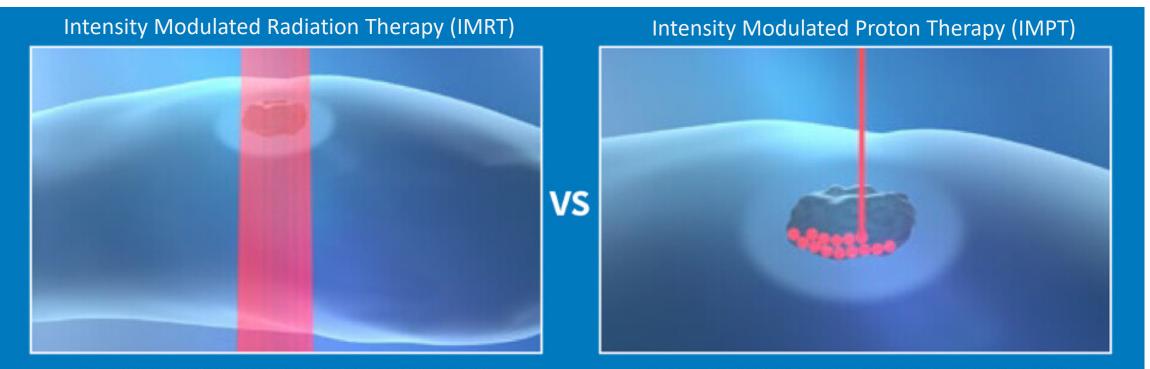
Robert Rathbun Wilson, Harvard University Radiological use of fast protons, Radiology **47**, 487-491 (1946) doi:10.1148/47.5.487.



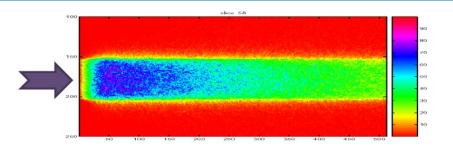


23

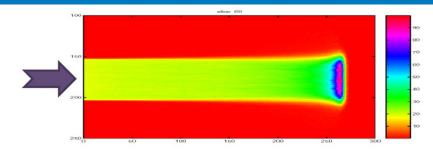
The TPPT Project: Proton Therapy (PT)



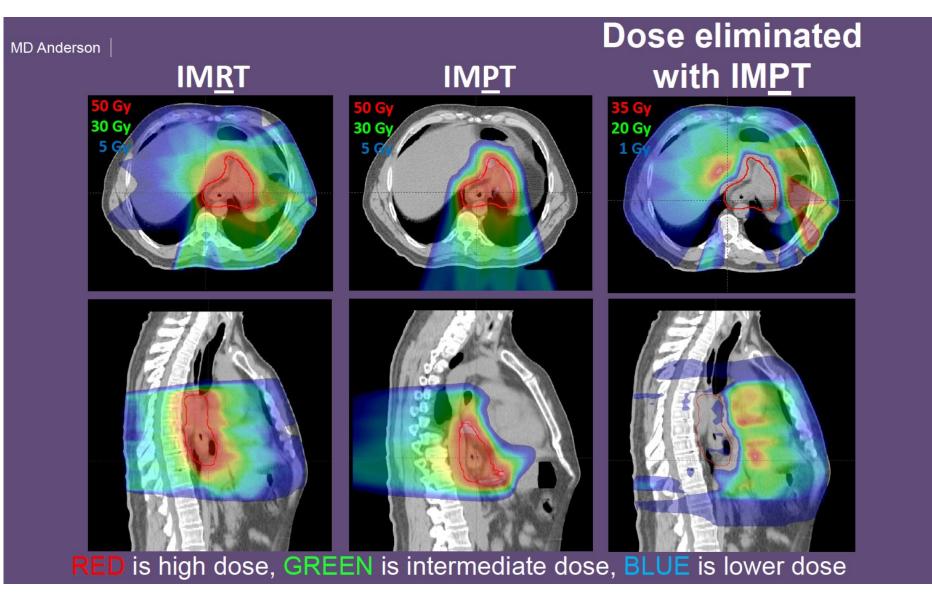
Traditional X-ray (produces exit dose)



Proton Therapy (produces no exit dose)



The TPPT Project: Protons vs. Photons

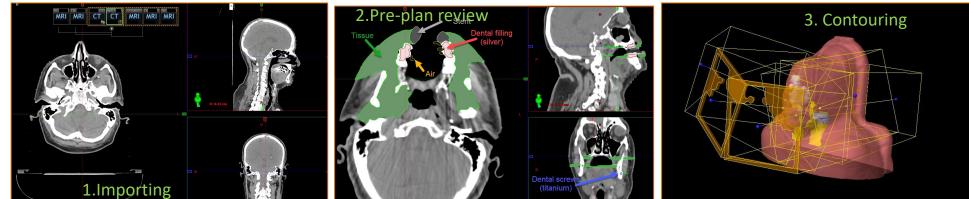


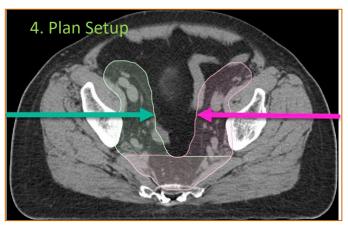
The TPPT Project: Treatment Planning

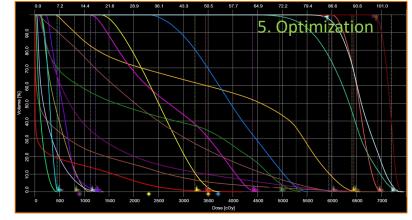


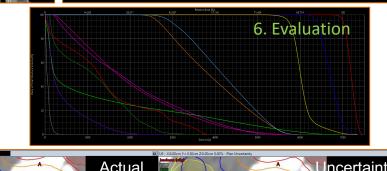
Making Cancer History®

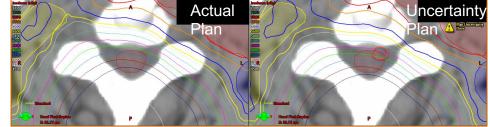
- Meticulous and sophisticated treatment planning ("well-oiled machine") 5 days of intense preparations
 - 1. Importing
 - 2.Pre-plan Review
 - 3.Contouring
 - 4.Plan Setup
 - 5.Optimization
 - 6.Evaluation
 - 7.Summary











From Christine Chung, MS, CMD, Research Dosimetrist

The TPPT Project: Issues Facing PT

- Anatomy changes may perturb dose distributions to a significantly greater extent for protons than for photons
- High gradients in proton dose distributions are very sensitive to anatomy motion and changes, and to set up variations
- Gaps in the knowledge of relative biological effectiveness (RBE) of protons
 - Proton RBE is assumed to be a constant of 1.1
- Heterogeneity in patient population, tumor characteristics and treatment techniques may be obscuring the potential advantages of protons for subpopulations of patients
- Evolving treatment delivery and planning systems and techniques
- Limits to the applicability of knowledge and models based on photon therapy experience to protons
- High cost of proton therapy

A successful plan requires good communication and multitude of factors that need input from:

- Physician
- Dosimetry team
- Physics team
- Therapy team

Much room for improved feedback of ongoing therapy (a.k.a. proton range verification)

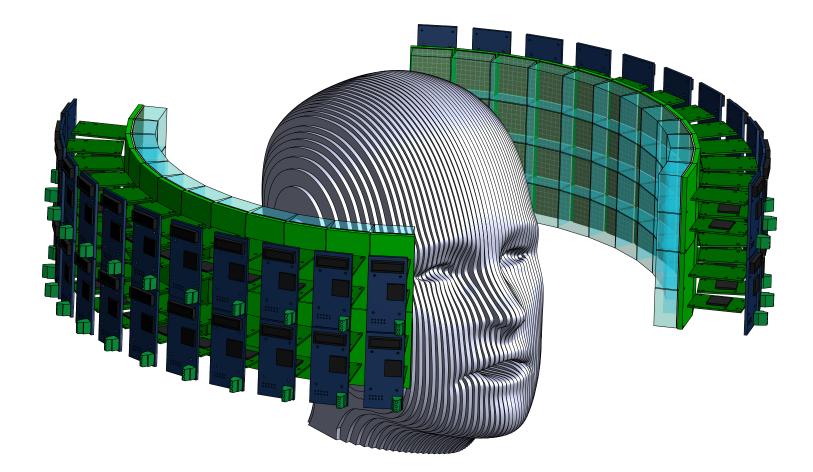
From Radhe Mohan, PhD



MDAnderson Cancer Center

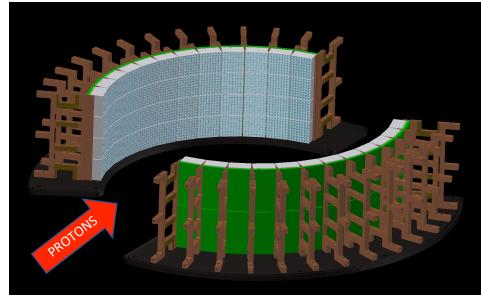
Making Cancer History[®]

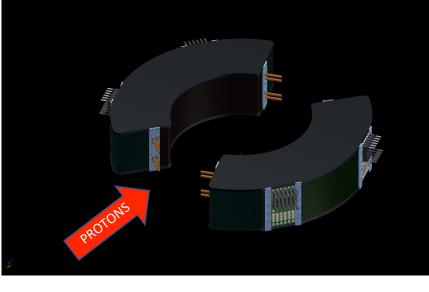
The TPPT Project: Meet the TPPT Scanner



The TPPT Project: Scanner Design

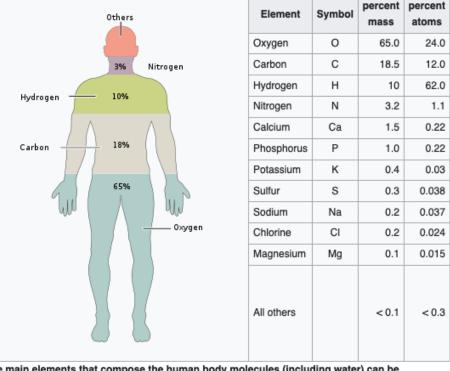
- Design Goal:
 - Detect positron emitting species (PES) activated by beam
 - Short lived, no time for conventional PET scan
 - 15min compared to 30min 1hr acquisitions
 - Give feedback on where protons are interacting \rightarrow range verification
 - Bonus: no added dose to patients since using beam activations
- Design Constraints:
 - High sensitivity \rightarrow "Do more, with less"
 - Shorter acquisition, fewer events
 - ToF greatly helps in this!
 - Beam optimized geometry → gap for proton delivery, detector is "live" during irradiations
 - Veto for beam spill, high-rate environment
 - Needs to be compact to fit into existing infrastructure





PES = positron emitting species Proton beam 511 keV ¹⁵₈C ¹⁵₇N + ⁰₊₁e Two anti-parallel 511 keV Photons produced 180° T___~ ~ 10 min 1/2 Unstable parent e Positron combines with nucleus electron and annihilates 511 keV Proton decays to neutron in nucleuspositron and neutrino emitted

The TPPT Project: PES



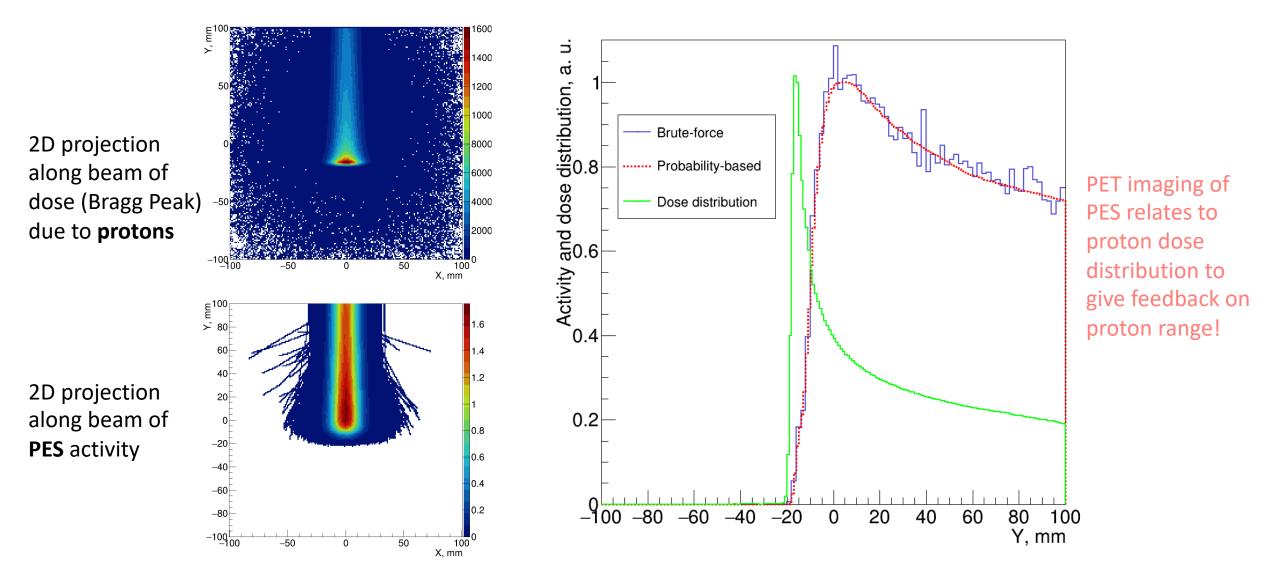
The main elements that compose the human body molecules (including water) can be summarized as CHNOPS.

Studenski MT et a/. Proton therapy dosimetry

Table 1	Relevant	positron	emitter	reactions	in	tissue	from
proton th	ierapy						

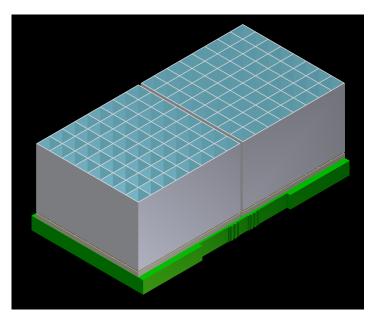
Reaction	Threshold energy (MeV)	Half life (min)	Positron energy (MeV)
¹⁶ O(p, pn) ¹⁵ O	16.79	2.037	1.72
¹⁶ O(p, α) ¹³ N	5.66	9.965	1.19
¹⁴ N(p, pn) ¹³ N	11.44	9.965	1.19
¹² C(p, pn) ¹¹ C	20.61	20.390	0.96
¹⁴ N(p, α) ¹¹ C	3.22	20.390	0.96
¹⁶ O(p, αpn) ¹¹ C	59.64	20.390	0.96

The TPPT Project: Proton Range Verification



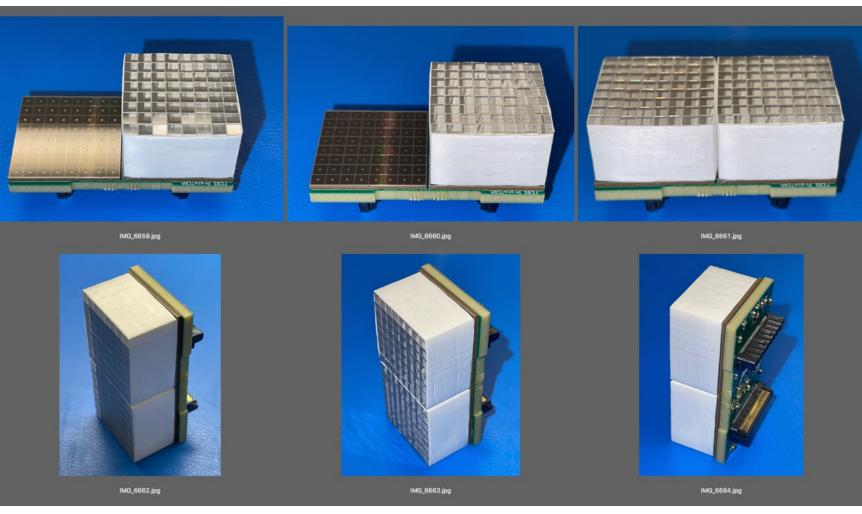
The TPPT Project: The Basic Building Blocks

3 x 3 x 15 mm³ LYSO^{*} crystals



1:1 coupling to Hamamtsu SiPMs Two 8 x 8 arrays

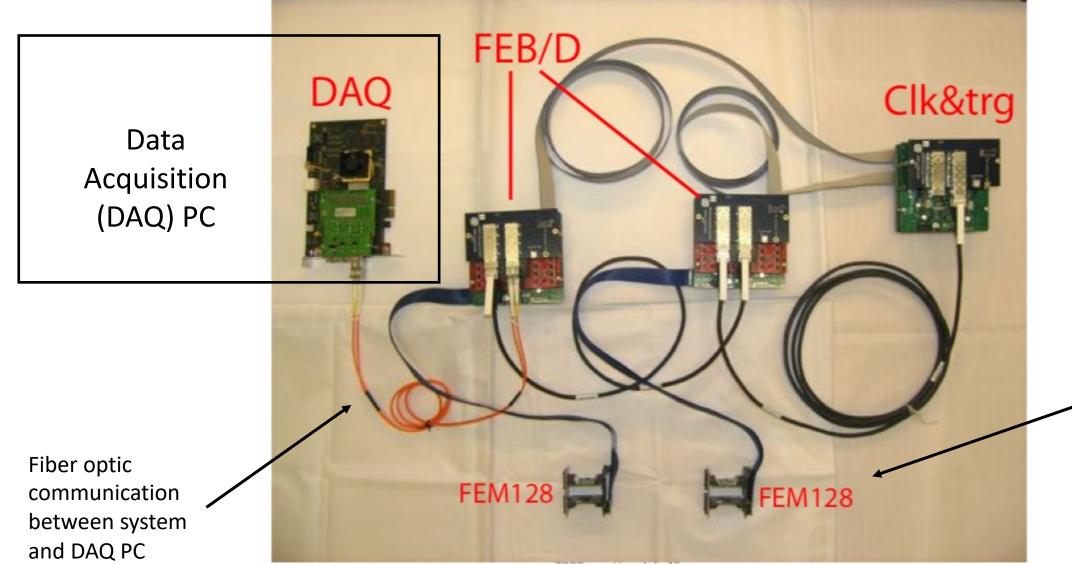
This is a PET optimized MPPC Array



*LYSO (Lu ^{1.8}Y ²SiO⁵Ce) is a Cerium doped Lutetium-based scintillation crystal

The TPPT Project: PETsys Electronics

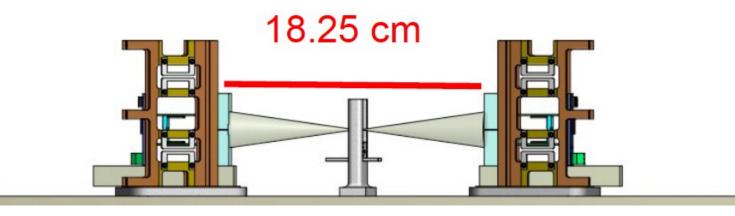


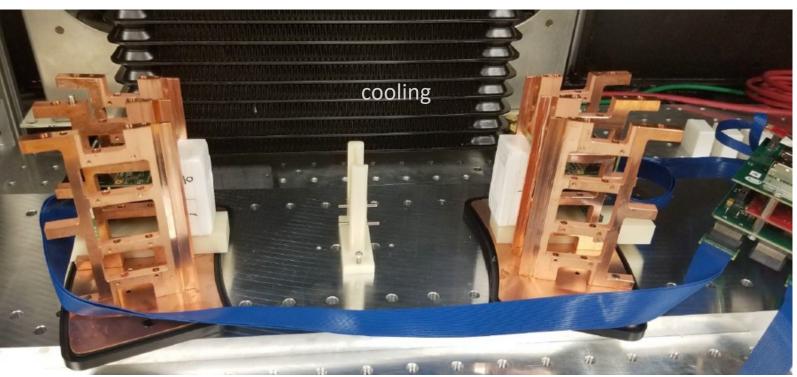


6144 total channels

The TPPT Project: Mini-PET

- Characterization and evaluation of all modules after gluing
 - Quality assurance
- Each module placed opposite a reference module
- Na-22 source for coincident gammas
- Extraction of early performance parameters (energy resolution and coincidence time resolution)
 - Next slides

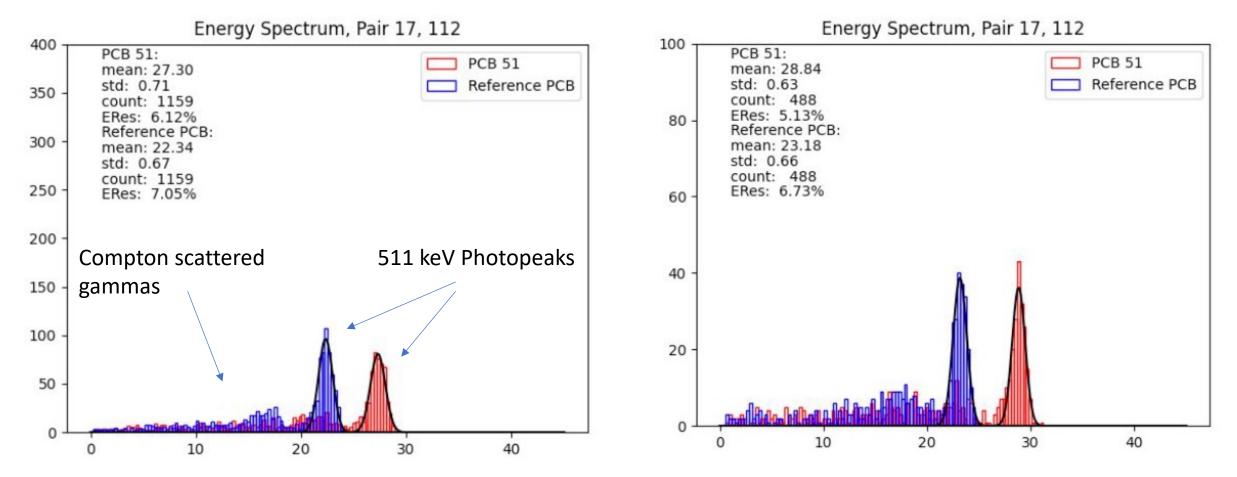


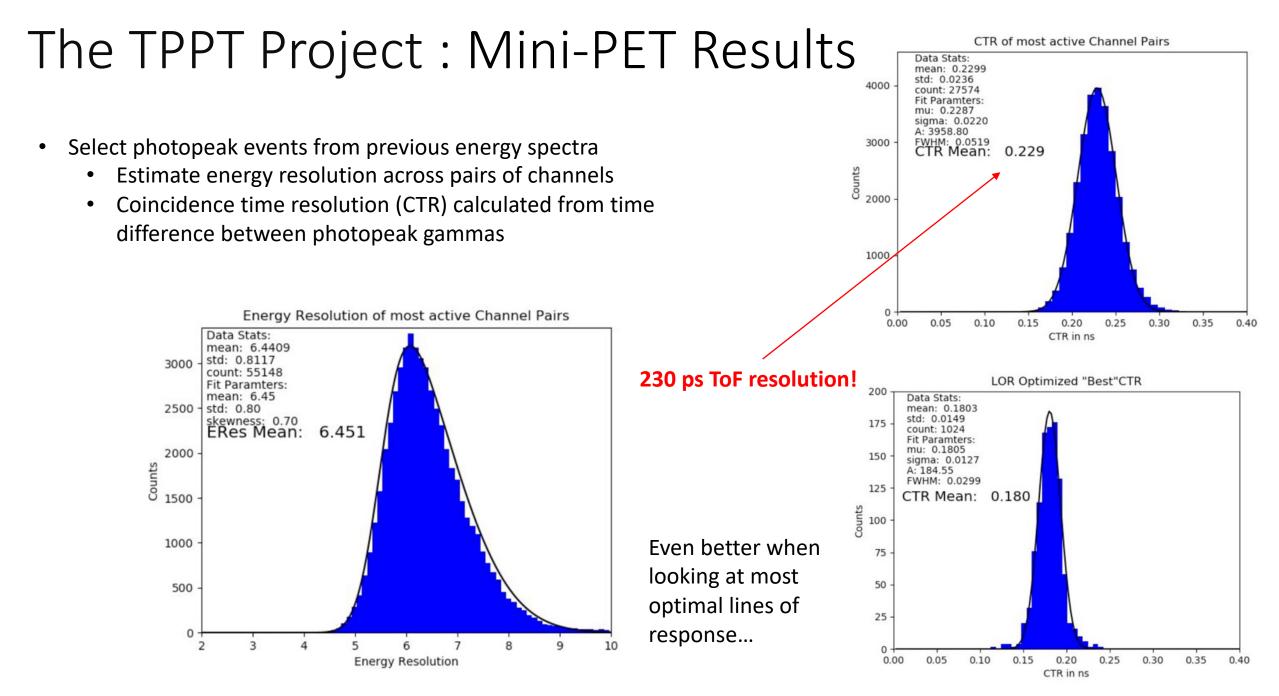


The TPPT Project: Mini-PET Evaluation



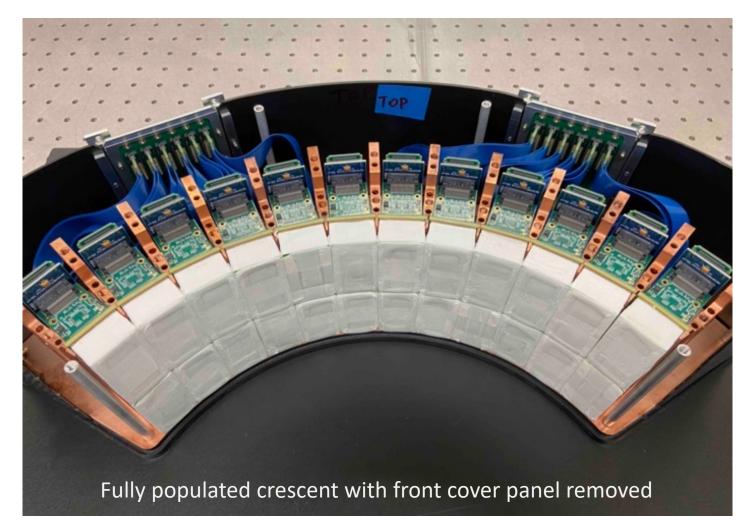
Ge-68

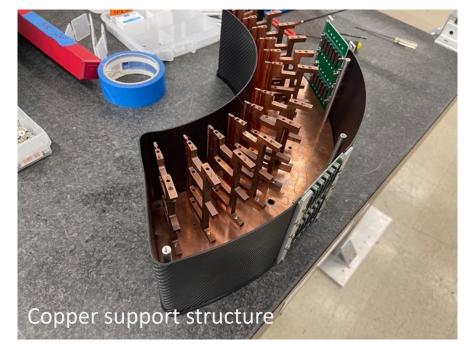




The TPPT Project : Assembly

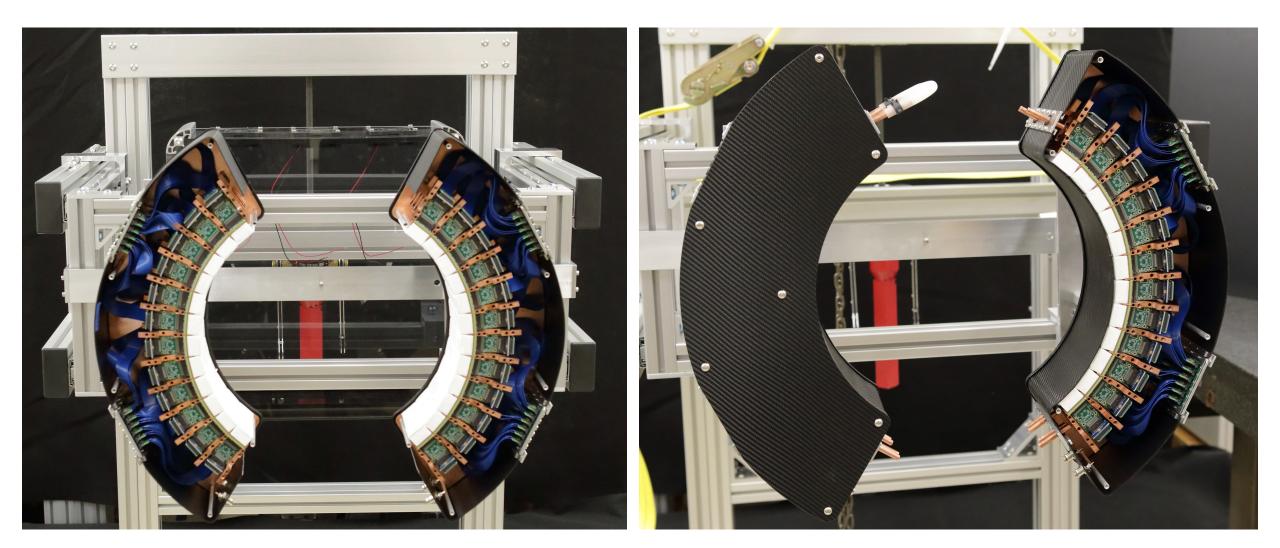
• The scanner at various stages of construction





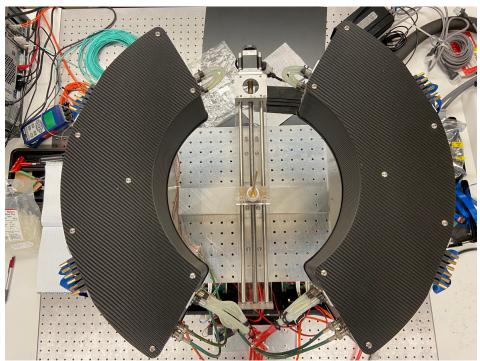


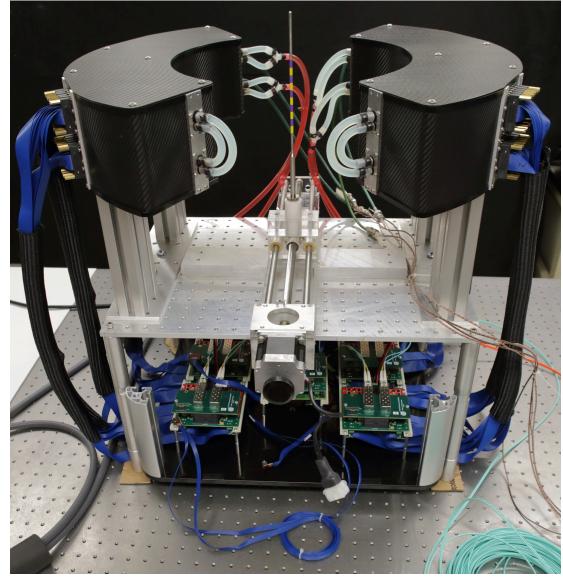
The TPPT Project : Full Scanner on Gantry



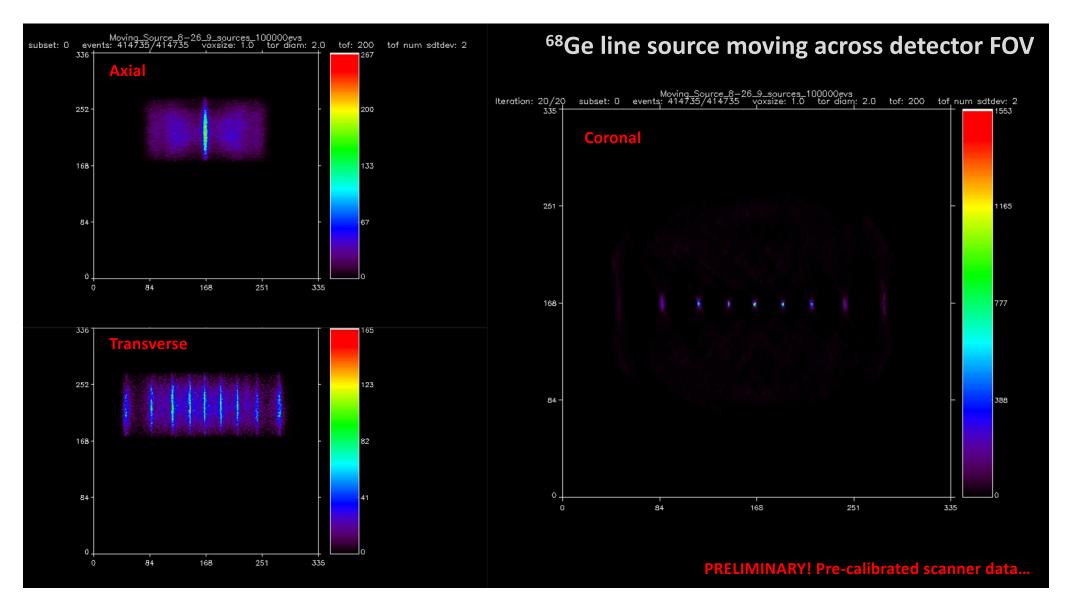
The TPPT Project : Full Scanner on Test Bench

- Various calibrations performed (or in the process):
 - SiPM OV and ASIC threshold scan
 - Normalization + Time alignment
 - Requires moving line source (⁶⁸Ge)
 - Cooling studies
 - DAQ stress testing
 - Image reconstruction debugging





The TPPT Project : First Reconstructed Images!



phantoms to characterize **PES production and** BEAM detection

Comparison with simulations ٠

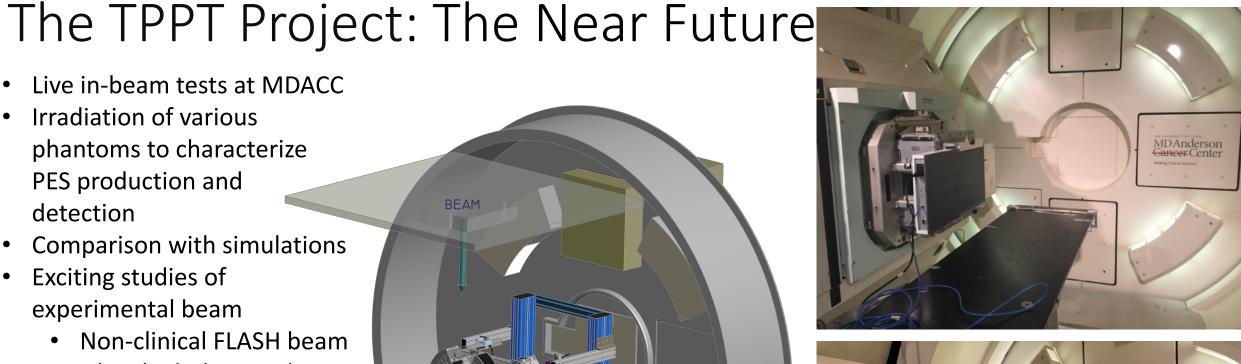
Live in-beam tests at MDACC

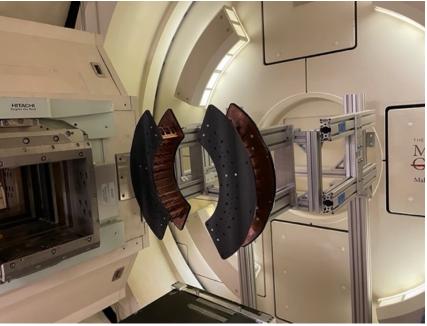
Exciting studies of ٠ experimental beam

Irradiation of various

- Non-clinical FLASH beam
- Ultra-high dose and • dose rates

Design drawings by Marek Proga





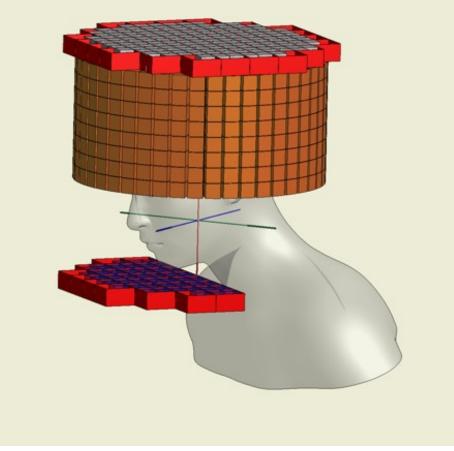
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Future Ideas

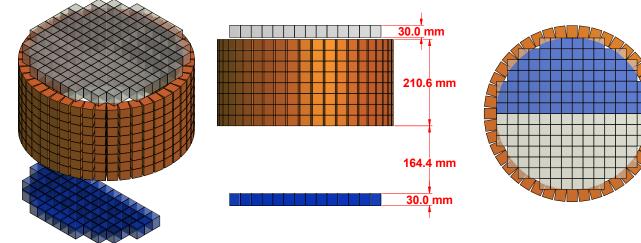
Novel PET ideas only achievable thanks to SiPMs

Future Ideas: C³-PET



Design and modeling of a high resolution and high sensitivity PET brain scanner with double-ended readout

Christopher Layden^{1,*}[©], Kyle Klein¹, William Matava¹[©], Akhil Sadam¹[©], Firas Abouzahr¹[©], Marek Proga¹, Stanislaw Majewski², Johan Nuyts³[©] and Karol Lang¹



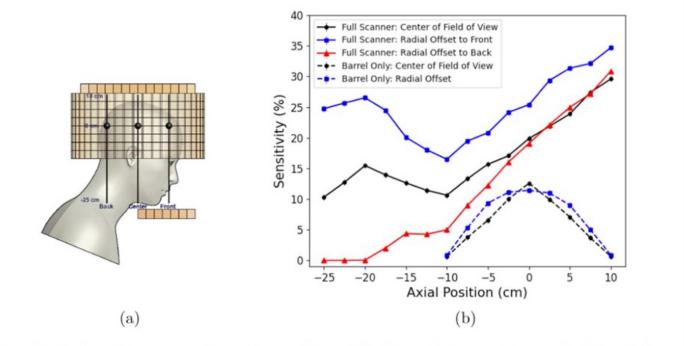
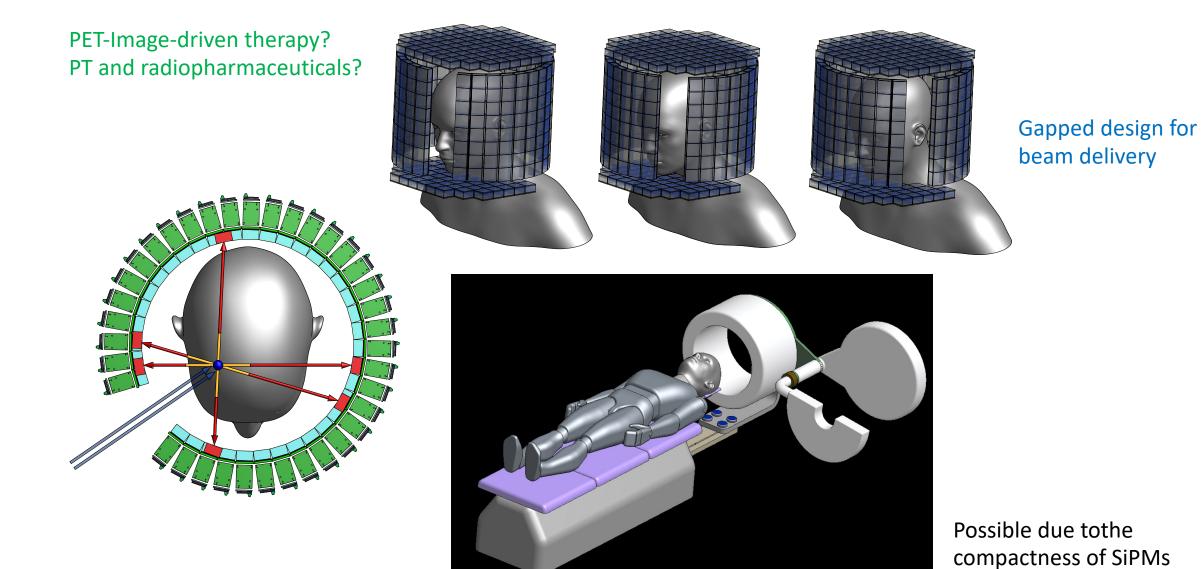


Figure 3. (a) Positions of line sources used for sensitivity predictions. (b) Absolute sensitivities for point sources placed along the line sources, for both the full scanner and barrel module alone, at the center of the radial field of view and at 10 cm radial offsets.

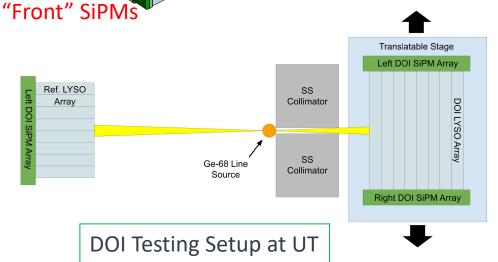
Future Ideas: C³-PET for Proton Therapy

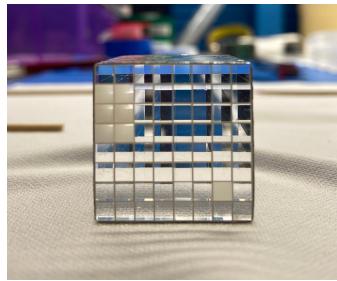


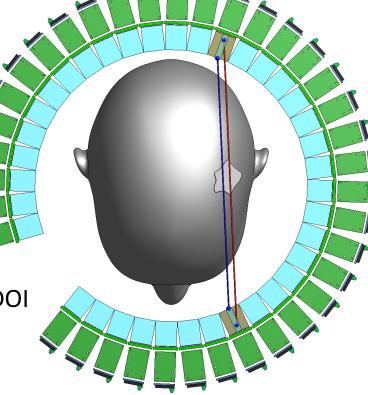
Future Ideas: DOI PET

"Rear" SiPMs

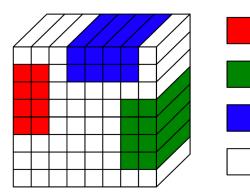
- Goal: Obtaining depth-of-interaction (DOI) information from PET systems
- Sandwich crystals between SiPMs
- Use relative intensities to extract DOI
- Helps eliminate parallax error
- Potential to greatly improve image quality
- Studying optical properties that can enhance DOI







Example of parallax error resulting in shifted LOR



14 μm LYSO 28 μm LYSO 4 μm LYSO

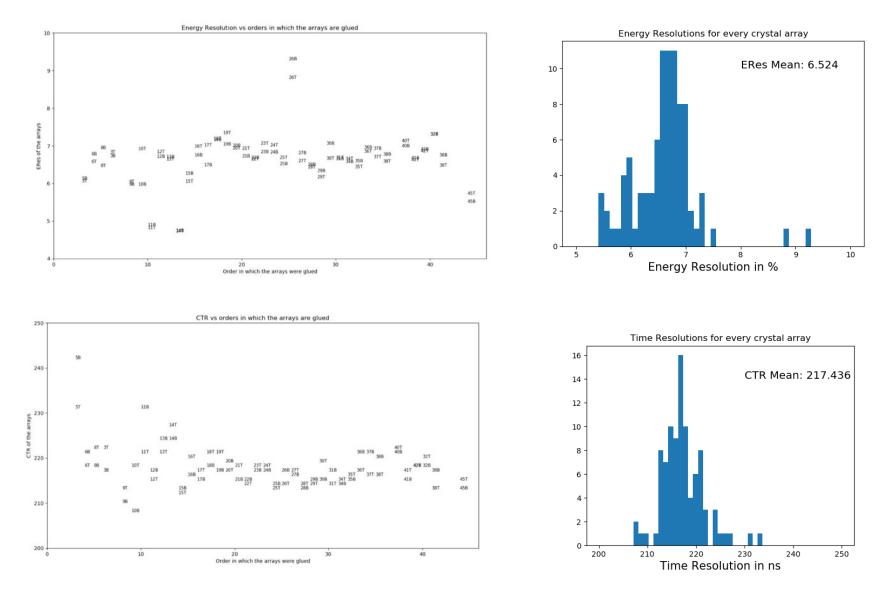
Polished LYSO

Summary and Conclusions

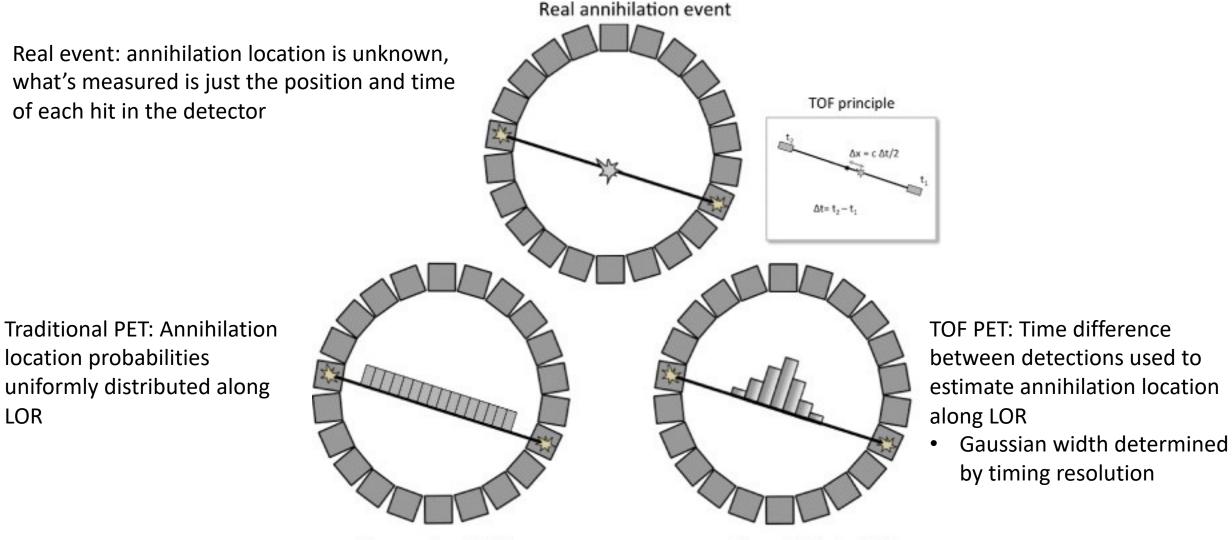
- Physicists <u>CAN</u> help fight cancer!
 - Medical professionals are incredibly valuable and talented but also very busy!
 - We can apply our long history and expertise in detector technology to advance the field
 - Help improve treatment outcomes for PT patients
- ... And SiPMs have been crucial in this effort!
 - They offer numerous advantages over PMTs in PET imaging:
 - Fast timing, pixelization, compactness, functionality in magnetic fields fields (for integration with MRI)
 - Can be used to create novel scanner designs to push PET into new territory
- The TPPT Scanner is one such example of a next-gen SiPM-based PET system
 - It has been designed, assembled, and almost fully commissioned
 - Just some last calibration steps remaining
 - We will move it to MDACC later this year to begin taking in-beam data
- The project has excited us to continue working in PET and medical imaging

Backup Slides

The TPPT Project : Mini-PET Results



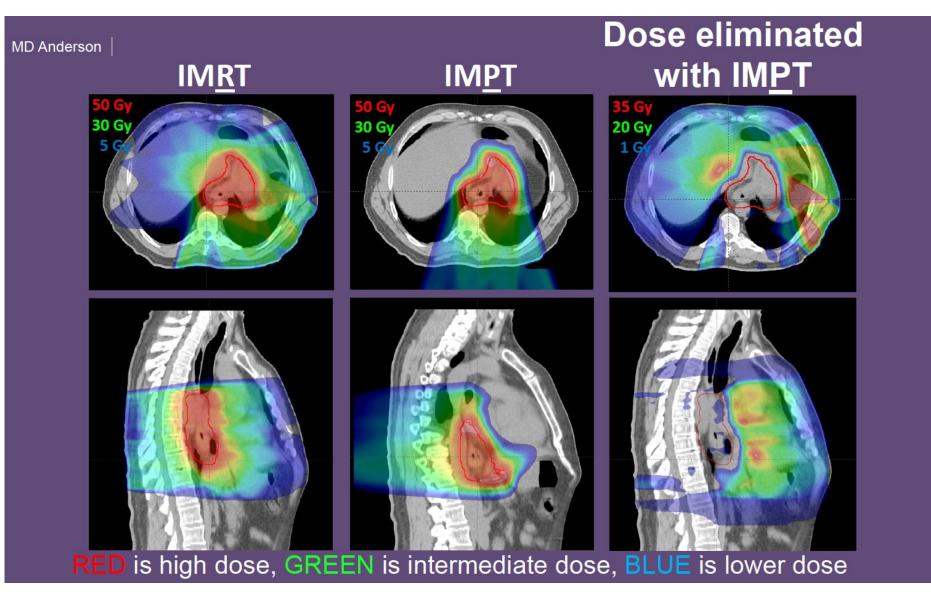
PET Imaging: Time-of-Flight PET



Conventional PET

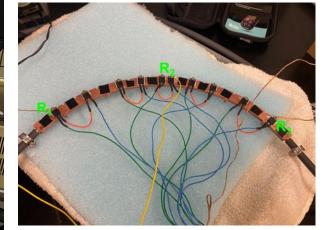
Time-Of-Flight PET

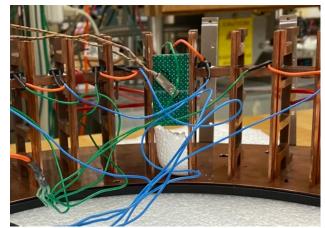
Radiation Therapy: Protons vs. Photons

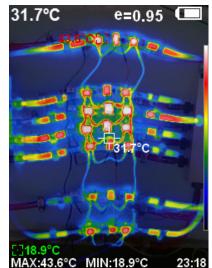


TPPT Hardware: Cooling System

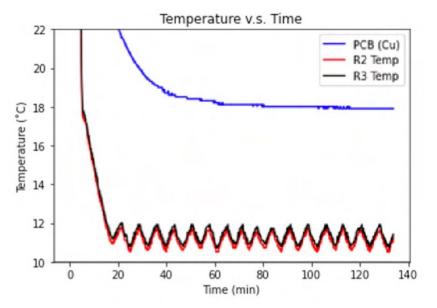




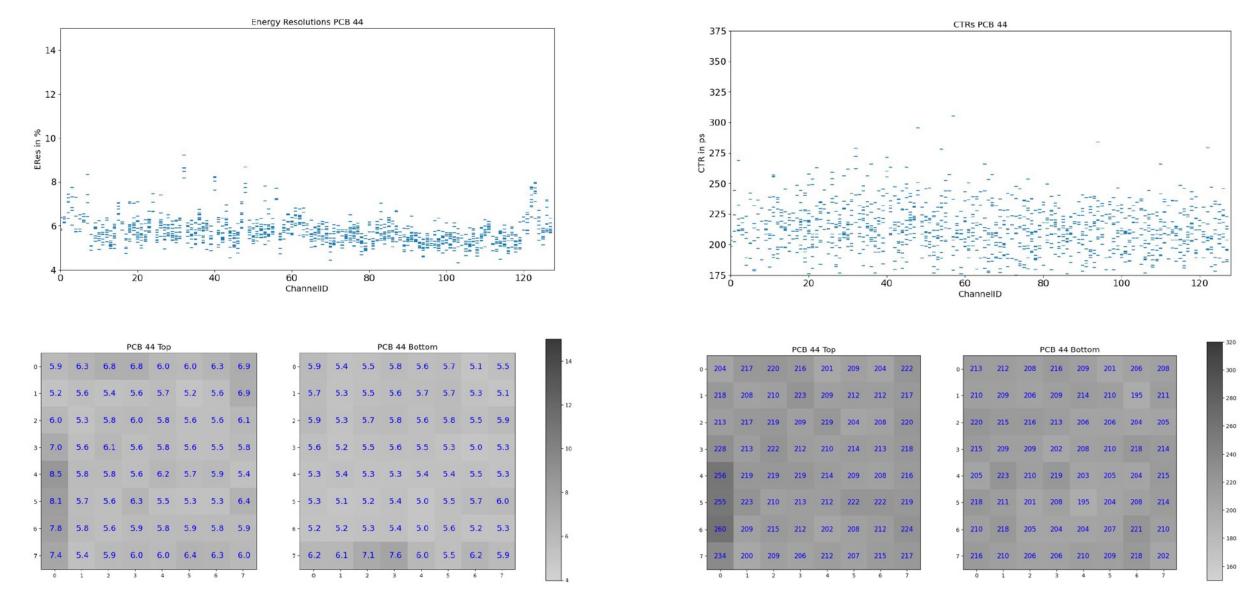




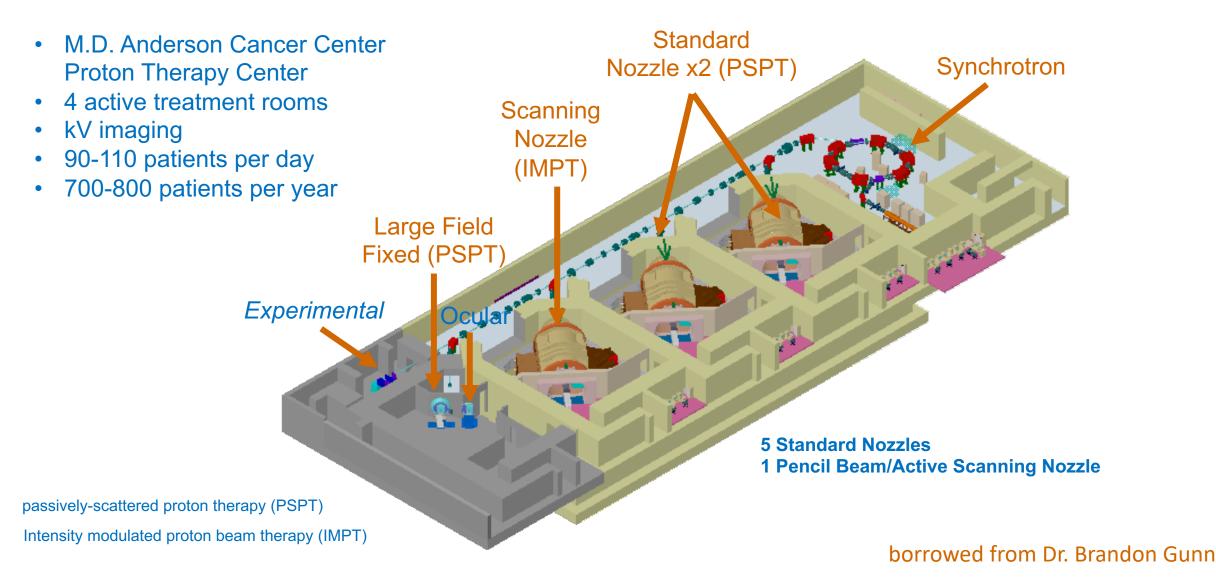
- ~1W dissipation per ASIC (2 x ASIC p module, 96 total)
- ASICs require stable temperature for calibration and operation
- Developed custom liquid cooling system
 - Copper elements circulate coolant and make thermal contact with ASICS and internal structure



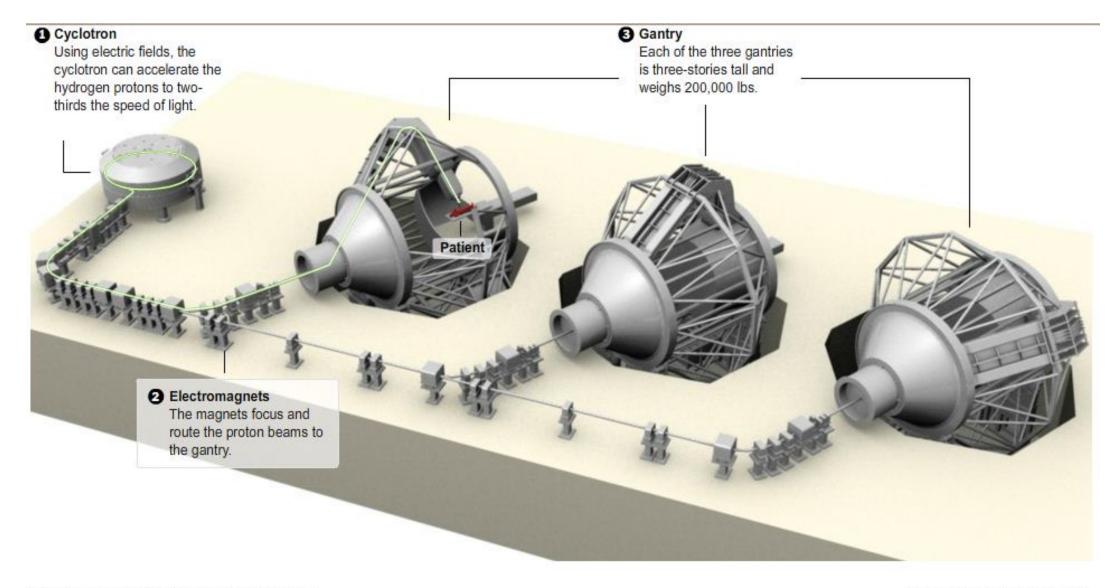
The TPPT Project : Mini-PET Results



Proton Therapy: MDACC Beamline



Proton Therapy: The scale ...



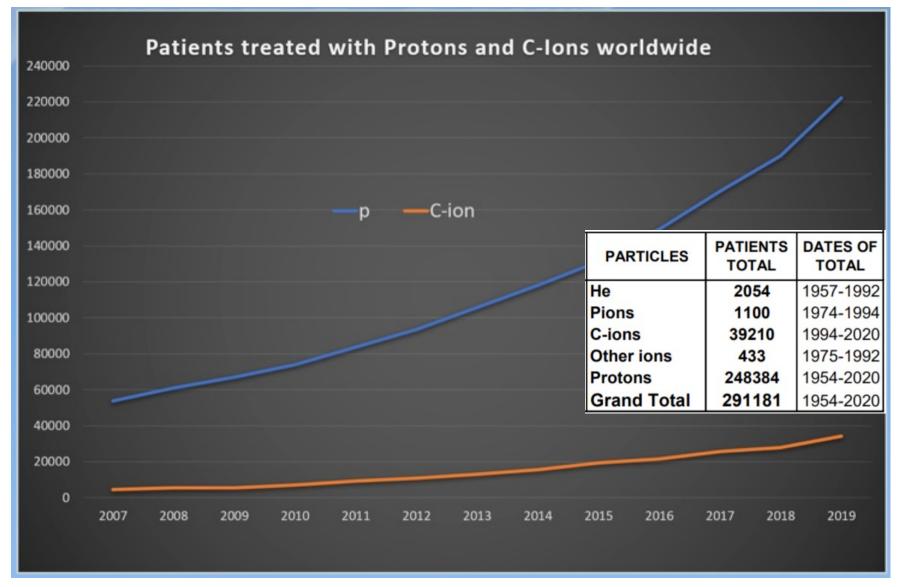
Sources: University of Florida Proton Therapy Institute

Proton Therapy: On the rise....



- 42 facilities in the USA 26 in Japan ... 7 in Germany ... 7 in China ... (3 Netherlands)
- 2 in Texas: MD Anderson CC and at UT Southwestern Medical Center
- 1 more to open soon at MD Anderson

Proton Therapy: On the rise....



The TPPT Project: Inception

- 3 years ago we formed a consortium to compete in the UTAustin Portugal funding competition
- The consortium includes
 - U. of Texas MD Anderson Proton Therapy Center

Sahoo Narayan, Falk Poenisch, David R. Grosshans

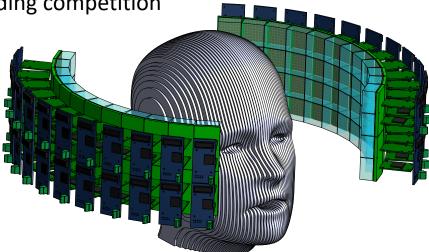
• U. of Texas at Austin

Karol Lang, Marek Proga, +

• **PETsys Electronics**

Vasco Varela, João Varela, Stefaan Tavernier, Ricardo Bugalho, Luis Ferramacho, Miguel Silveira, Carlos Leong, Jose da Silva

- LIP, Laboratorio de Instrumentação e Fisica Experimental de Particulas (Coimbra) Paulo Crespo, Mario Pimenta, Patricia Goncalves, Hugo Simões, Andrey Morozov
- Centro de Ciências e Tecnologias Nucleares (C²TN), Instituto Superior Técnico (Lisbon)
 António Paulo, Fernanda Marques, Paula Raposinho, Joana Guerreiro, Filipa Mendes, Salvatore di Maria, Maria Paula Campello
- Instituto de Ciências Nucleares Aplicadas à Saúde (ICNAS), Universidade de Coimbra Nuno Ferreira, Francisco Caramelo, Antero Abrunhosa
- We proposed a "feedback" PET scanner to register nuclides activated in proton irradiations:
 - C-11 ($T_{1/2}$ =20min), N-13 ($T_{1/2}$ =10min), O-15($T_{1/2}$ =123sec)





LYSO vs BGO Crystal Properties

Table 1.

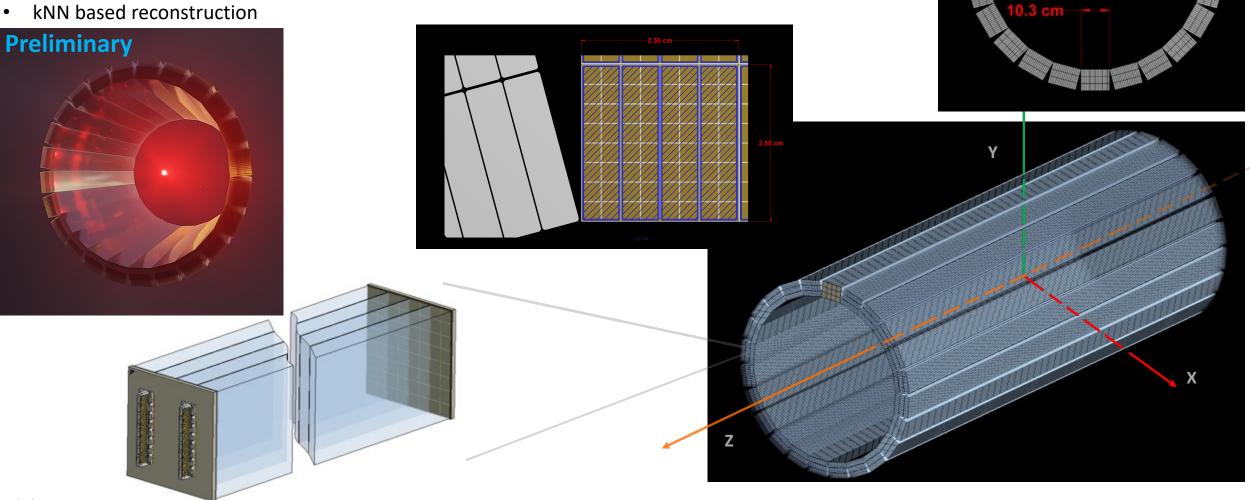
Properties of LYSO and BGO (from Saint-Gobain 2014, 2017).

	LYSO	BGO
Effective atomic number (Z _{eff})	60	74
Density (g cm $^{-3}$)	7.1	7.13
Attenuation length for 511 keV (cm)	1.2	1.0
Light yield (photons MeV ⁻¹)	8000-10 000	30 000
Decay time (ns)	37–45 ns	300
Peak wavelength (nm)	420	480

Image courtesy of doi: <u>10.1088/1361-6560/abc365</u>

Future Ideas: Full Body PET

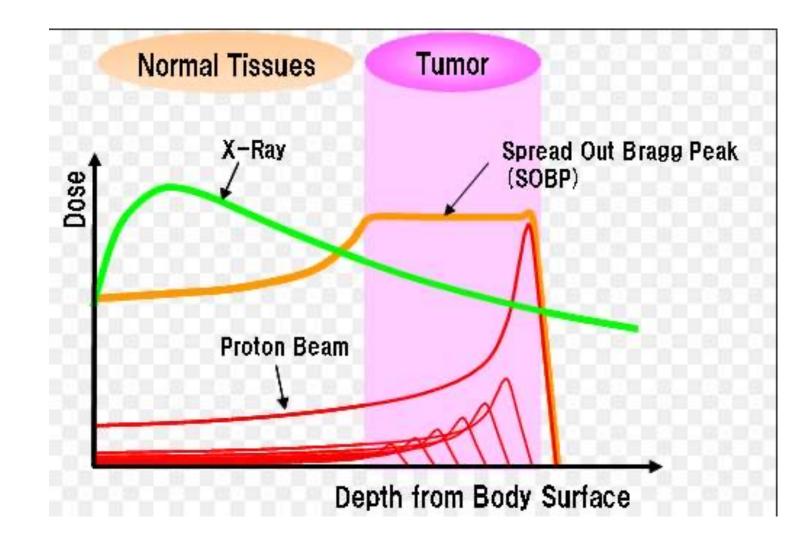
- 1m long barrel PET (2.54 x 0.62 x 100cm scintillator) •
- 1152 plastic scintillator strips and 576 SiPMs. ٠
- kNN based reconstruction ٠



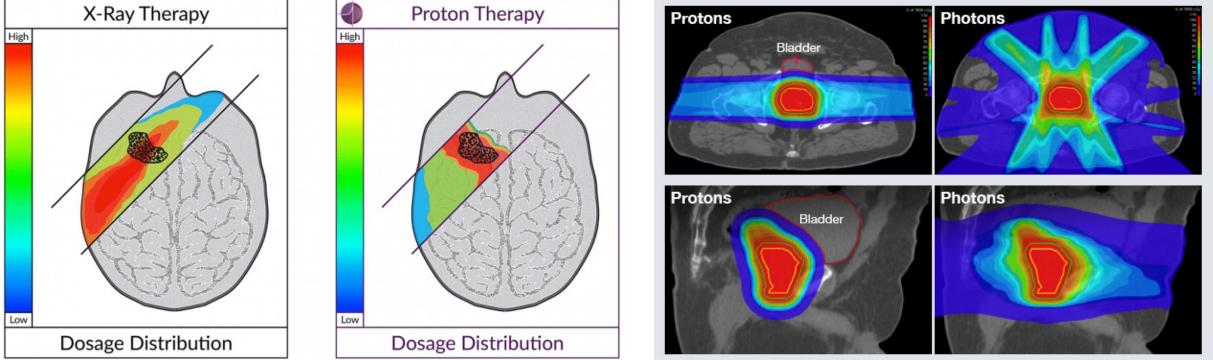
78.4 cm

IMPT

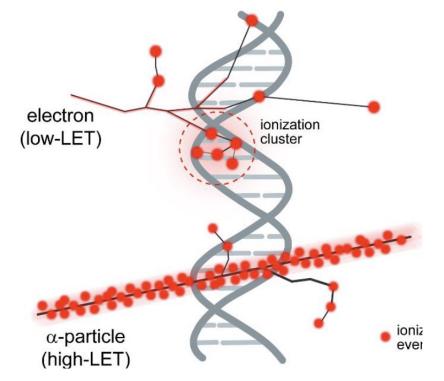
(Intensity Modulated Proton Therapy)



IMRT vs IMPT



Destroying cancer or impeding its growth



oxygen radicals ...

