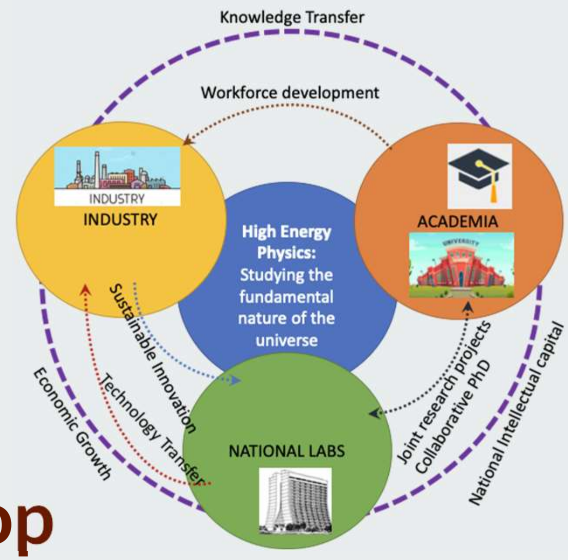
UltraFast & Precise External Beam Monitor for FLASH and Other Advanced Forms of Radiation Therapy



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January 27, 2021

FLASH Radiation Therapy Workshop

Breakout Session 4, Application Area 3:
Development of improved large-area, ultrafast radiation detectors for real-time FLASH-dose monitoring & FLASH imaging

Application and Industry (A&I) working group
Snowmass 2021: Community Engagement Frontier (CEF)

Collaboration: DOE, NIH, academia & industry

- Integrated Sensors, LLC, *Peter Friedman (NIH-NCI and DOE-NP SBIR funding)*
- University of Michigan, *Physics Dept & Medical School, Radiation Oncology*
  Daniel Levin, Nicholas Ristow, Claudio Ferretti (Physics) and Dale Litzenberg (Radiation Oncology)
- Loma Linda University, *Biomedical Engineering & Medical School*
  Reinhard Schulte and Vladimir Bashkirov
- Michigan State Univ. & DOE Facility for Rare Isotope Beams (FRIB)
  Thomas Ginter and Marco Cortesi
- Subcontractors in U.S. and Europe

FLASH vs. Conventional radiotherapy (RT)

- Conventional external beam radiotherapy (RT): patient typically irradiated for **1-2 minutes**, for **5 days/week**, for **1-2 months**.

- FLASH-RT: patient irradiated for **$<$0.1 second**, for **1-4 days**, resulting in:

  - Greatly reduced side-effects
  - Less tissue toxicity
  - Lower cost
  - Better patient satisfaction due to shortened treatment, etc.

Ultimate Problem – *Radiation induced toxicity*

- Conventional External Beam Radiotherapy (EBRT) is severely limited due to *radiation induced toxicities.*
- Radiation induced toxicities can be ***reduced*** by ***ultrafast*** delivery of radiation at dose rates ***orders-of-magnitude*** greater than used in conventional EBRT.
- This allows much higher radiation dose treatments and *increases the therapeutic index* over conventional radiation delivery.
- This is known as the "**FLASH effect**".

Major Problem – *Monitoring FLASH delivery*

- FLASH is ~***1000*** times faster with ***order-of-magnitude*** higher dose (e.g., ***≥ 40 Gy***) than conventional-RT

- FLASH dose is delivered in **< 100 ms**. For *proton*-FLASH the corresponding beam luminosity for this dose is ~$\boldsymbol{10^{12}}$ ***protons/cm***$^{\boldsymbol{2}}$ ***s***

- ***Standard dosimetry methods <u>do not work</u>*** at the radiation intensity of FLASH delivery

Solution – *UFT™ beam monitor for FLASH-RT*

- Ultra-Fast & Transmissive (**UFT™**) beam monitor:
  Integrated Sensors (**I-S**) ***patented*** materials & designs *continuously* analyzes FLASH beam every **0.1 ms** as patient is irradiated.

- Total *water-equivalent thickness* of **UFT™** beam monitor for FLASH beam with 100-200 MeV protons is **0.5 mm**, possibly less.

- **UFT™** beam monitor spatial resolution is **~ 0.01- 0.1 mm**, depending upon beam intensity, integration time, and energy.

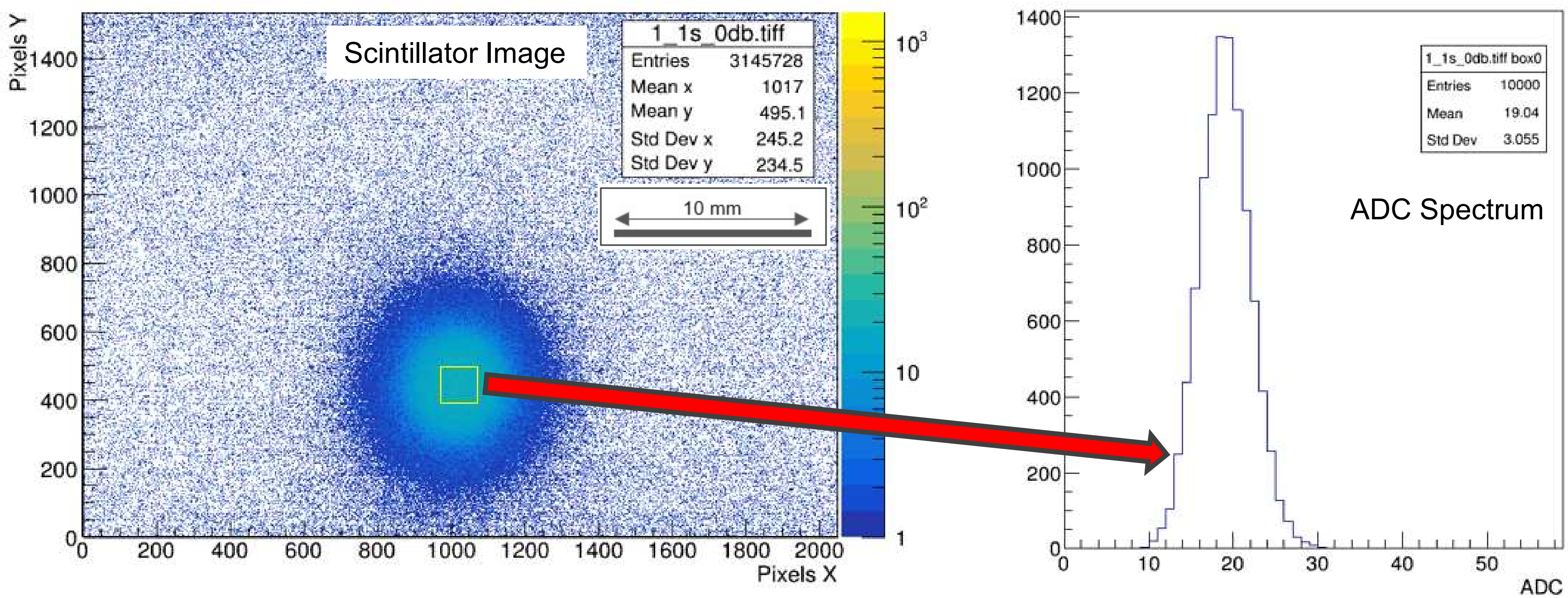
Benefits: *NIH-NCI (Cancer) & DOE-NP (Physics)*

- NIH-NCI funded beam monitor program demonstrated FLASH-RT capability for **electrons, protons, photons/X-rays** and **carbon-ions**. Can also measure **transient particle spikes** of **1-100 μs** from synchrotrons.

- Funded NIH-NCI and DOE-NP programs led to I-S patented **UFT™** beam monitoring technology including *novel scintillator* materials for FLASH-RT and beamline tuning at the DOE Facility for Rare Isotope Beams (FRIB).

- **UFT™** ***high-vacuum*** beamline monitor to be demonstrated at FRIB in 2021. System to monitor beam position, shape and luminosity for all nuclei up to **U-238**, over range from **~ 1×10^{0} to 10^{11} pps**.

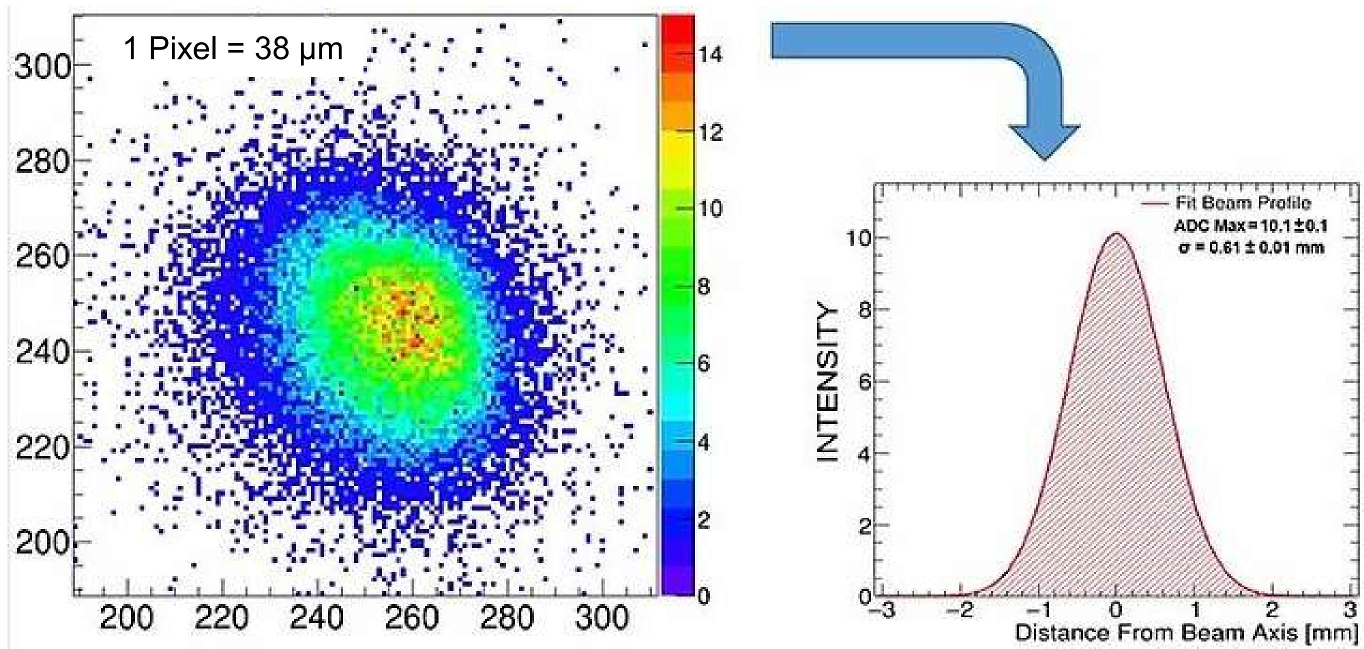
Results* with *electron*-beam: ^{90}Sr (~1 MeV beta's)*



__(Left)__ - Image exposure = <u>1 sec</u>. Source luminosity at scintillator surface = __<u>6.9 x 10^5 electrons/cm^2-sec</u>__.

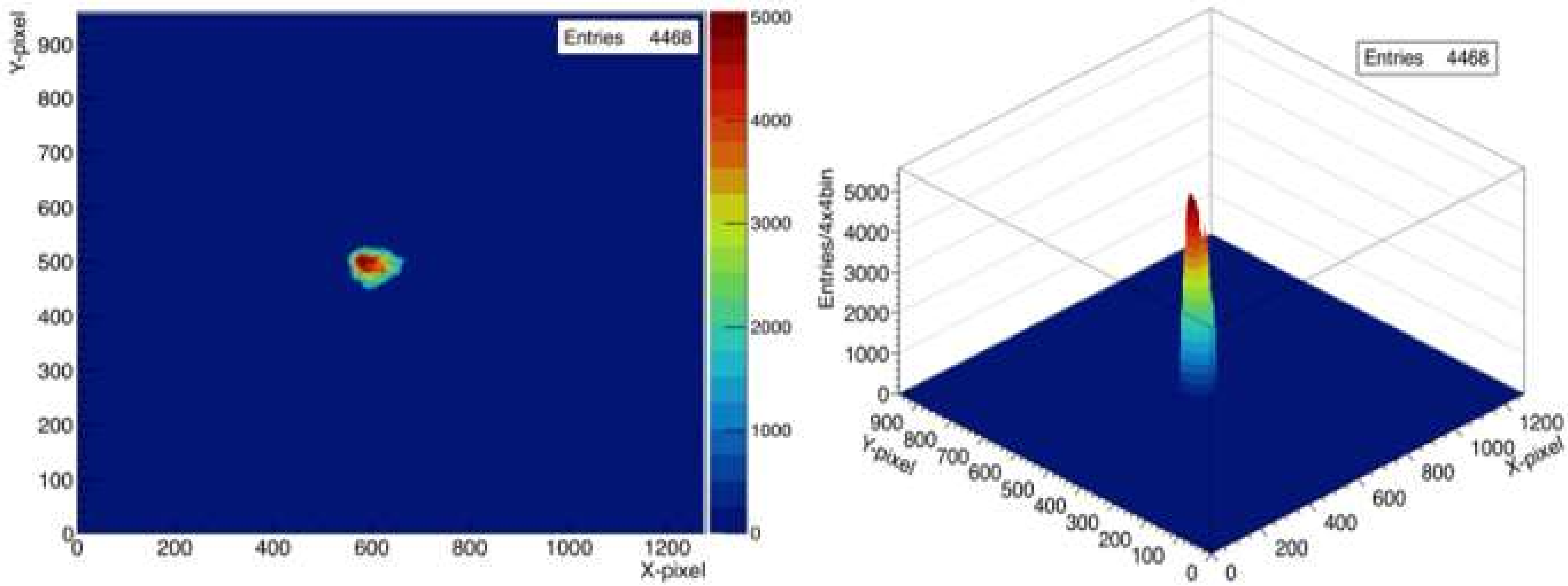
***(Right)** - ADC spectrum for 100 x 100 pixel fiducial box (1.9 x 1.9-mm)*

Results for static ***proton***-beam at low acceptance



(Left) *– Proton beam irradiating a 191 µm thick scintillator with* ***<u>1 ms</u>*** *shutter exposure.*
(Right) *– Figure is the Gaussian fitted plot of the* ***Left*** *beam image with a measured beam FWHM is 1.44 mm.*

Results for <u>80 mm/ms *scanning*</u> ***proton***-beam



(Left) *– Background suppressed image of ~2.5 mm diameter proton beam moving at 80 mm/ms, captured in* ***<u>10 µs</u>*** *(i.e. shutter speed). Beam intensity corresponds to* ***FLASH dose rate of 200 Gy/s****. Beam movement in 10 µs was 0.8 mm.* ***(Right)*** *– Same image as Left, but as a 3D plot with beam intensity profile data added.*

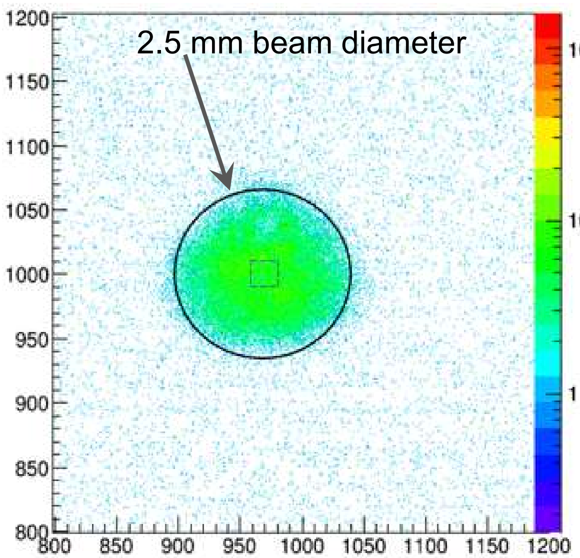
Radiation damage test results with *proton*-beam

Summary of MIBL Proton Beam Accelerated Test Results for 191 µm thick Scintillator

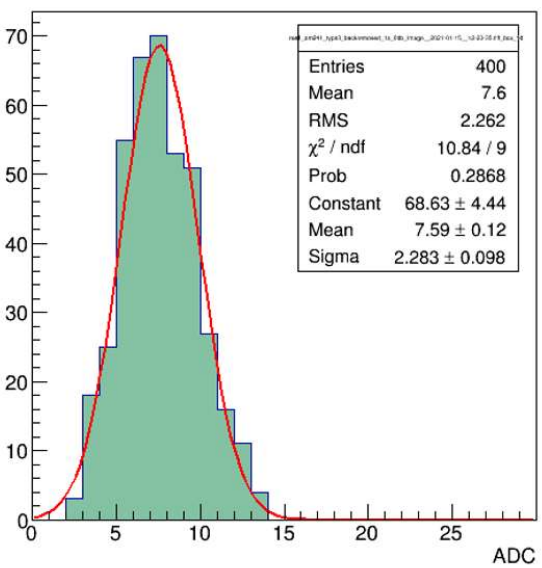
Dose Rate (kGy/s)	Beam Energy (MeV)	Total Dose (kGy)	Scintillator Rad-Damage Observations
0.11	5.4	33	No discoloration. Minimal rad-damage, **50% recovery in 4 hours**
0.20*	5.4	59	No discoloration**. Minimal rad-damage, largely reversible***
3.3*	5.4	390	**Manageable rad-damage**. Very slight darkening that eventually disappeared*
9.2	3.0	490	Unacceptable rad-damage. No ablation but rapid fluorescence decrease
92	3.0	6,100	Slow surface ablation and immediate fluorescence decrease
460	3.0	15,000	*Immediate fast* surface ablation, burning hole through 60-70% of scintillator
**Rates of 200 & 3,300 Gy/s with minimal rad-damage are well above that required for FLASH-RT*			

Delivered *continuous* dose of 59,000–390,000 Gy, at 200–3,300 Gy/sec (i.e. high-end of FLASH-RT) within 2-5 minutes in a single spot, with minimal to manageable scintillator degradation. Note that *59,000 Gy is equivalent to the full course of treatment for ~1,000 patients*.

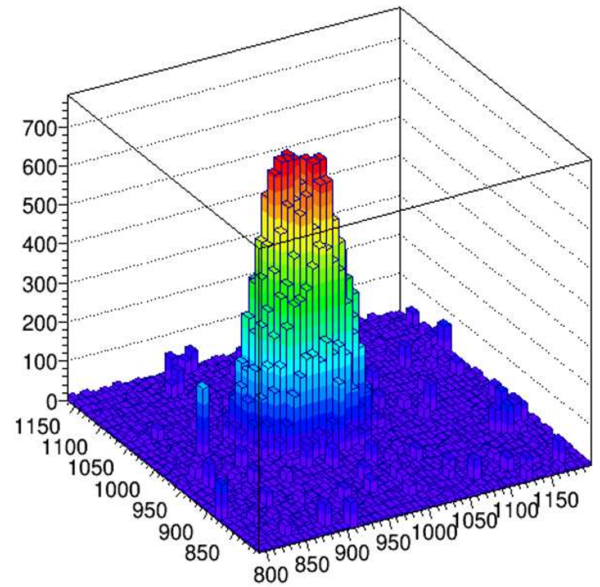
Results for low-luminosity static *alpha*-source



Alpha source beam image (^{241}Am)
(1 sec exposure, 7,000 pps rate)

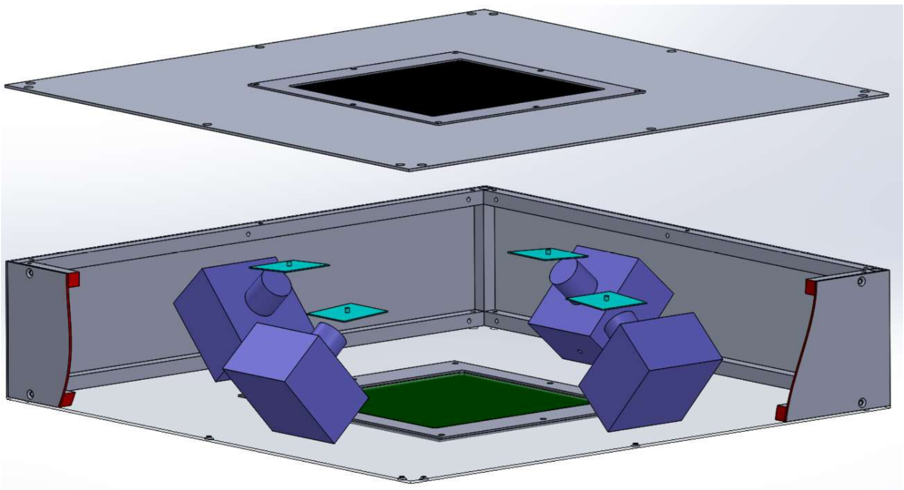


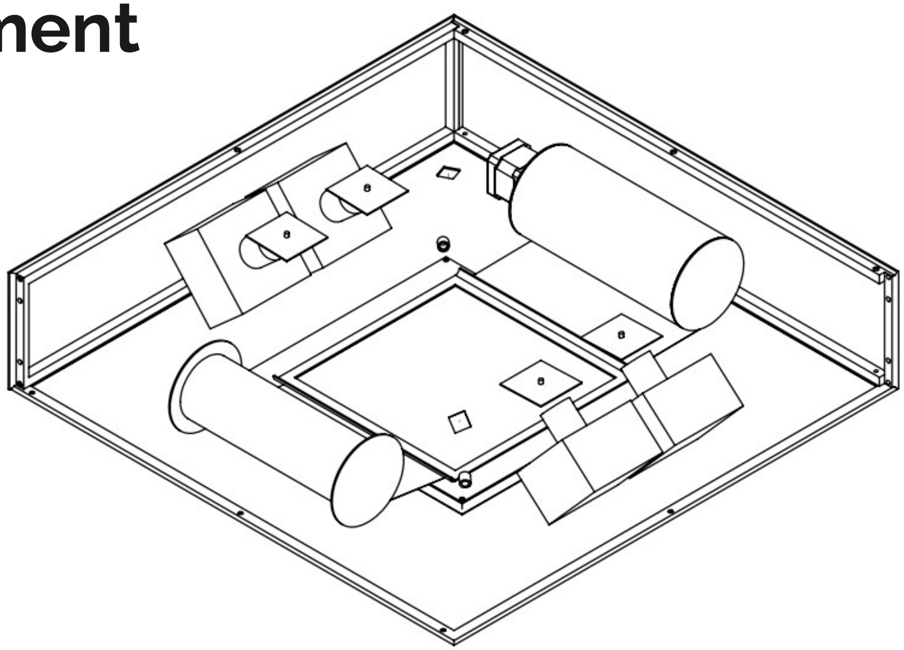
ADC histogram of peak
(distribution of 20x20-pixel peak fiducial box)

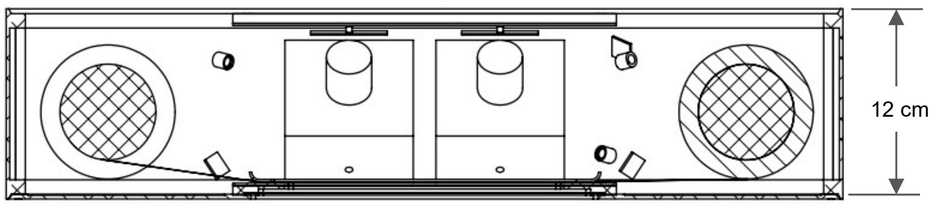


3D histogram of beam image
(rebinned pixel plot of full beam)

UFT™ beam monitor for FLASH-RT in ambient air environment







- Two ***patented*** I-S system designs with replaceable large-area scintillators (26 x 30 cm) and UV-LEDs & UV-photodiodes for internal calibration.
- Real-time **beam analysis** and **dosimetry** updated at 10,000 fps (i.e., 100 µs/image).

UFT beam monitor performance

Real-Time UFT™ Monitor Streaming Readout/Analysis: **0.1 ms**, continuous tracking of downstream ***beam position, intensity profile, movement, fluence/external dosimetry & angular divergence***.

Downstream UFT™ Monitor External Enclosure Depth (in beam direction): ***~ 5 inches***

"True" 2D-Position & Ultra-High Beam Profile Resolution: **~ 1 μm** *(depending on readout/update time)*

Proton Beam Energy Loss through UFT™ Monitor:

< ***0.30 MeV*** *(downstream)* at 70 MeV*, and ≤ ***0.03 MeV*** *(upstream, in vacuum)* at 70 MeV
< ***0.18 MeV*** *(downstream)* at 140 MeV*, and ≤ ***0.02 MeV*** *(upstream, in vacuum)* at 140 MeV
< ***0.14 MeV*** *(downstream)* at 210 MeV*, and ≤ ***0.01 MeV*** *(upstream, in vacuum)* at 210 MeV

*Proton Beam Gaussian profile, **σ = 3.500 mm**. Lateral Spread (σ) 70-cm downstream from nozzle due to monitor materials (1st column); due to air (2nd column); and due to monitor + air (3rd column)*:

at 70 MeV*:	≤ ***0.024 mm*** (monitor);	***3.875 mm*** (70-cm air);	***3.899 mm*** (monitor + 70-cm air)
at 140 MeV*:	≤ ***0.006 mm*** (monitor);	***3.612 mm*** (70-cm air);	***3.618 mm*** (monitor + 70-cm air)
at 210 MeV*:	≤ ***0.003 mm*** (monitor);	***3.550 mm*** (70-cm air);	***3.553 mm*** (monitor + 70-cm air)

**Calculated beam energy loss & lateral spread via TOPAS/Geant4 (http://www.topasmc.org/) simulations.*

UFT^{TM} beam monitor applications

- FLASH-RT (electrons, protons, photons/x-rays and ions)
- Real-time dosimetry resolution/accuracy should be ≤2%
- FLASH Intraoperative radiation therapy (Electron IORT)
- Synchrotron based Proton and Carbon-ion EBRT
- Spatially Fractional EBRT (Grid, Lattice, Minibeam, Microbeam)
- Boron Neutron Capture Therapy (BNCT – EBRT)
- Noninvasive FLASH Cardiac Ablation (for cardiac arrhythmia)
- Beamline Monitoring – high vacuum & ambient air environments

UFT^{TM} beam monitor FLASH-RT partners/test-sites

- **Looking for collaboration partners and development funding to demonstrate UFT^{TM} beam monitor under actual FLASH-RT conditions (e.g., with electron, proton and/or photon sources).**

- **First prototype time-line is ~ 1 year**