Novel Ionizing Radiation Detection Systems for Radiation Therapy Applications (Keynote)

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LOMA LINDA UNIVERSITY HEALTH

Many Strengths.
One Mission.

Funding Disclosures

- R01 grant from National Institute of Biomedical Imaging and Bioengineering (2011 – 2015)
- P20 grant from the National Cancer Institute (2015 – 2018)
- SBIR grants from the National Cancer Institute (2013 – 2015, 2015 – 2019, and 2010 – 2022)
- EU grant to the ANDANTE Consortium (2012 – 2015)
- EU grant to the BioQuaRT Consortium (2012 – 2015)
- Particle Therapy Cooperative Group grant (2018 – 2019)
- Binational Science Foundation U.S.-Israel grants (2009 – 2013 and 2014 – 2018)

Outline

» Problems
  - ~Range Uncertainty
  - ~RBE Uncertainty
  - ~Ultrafast monitoring for FLASH RT

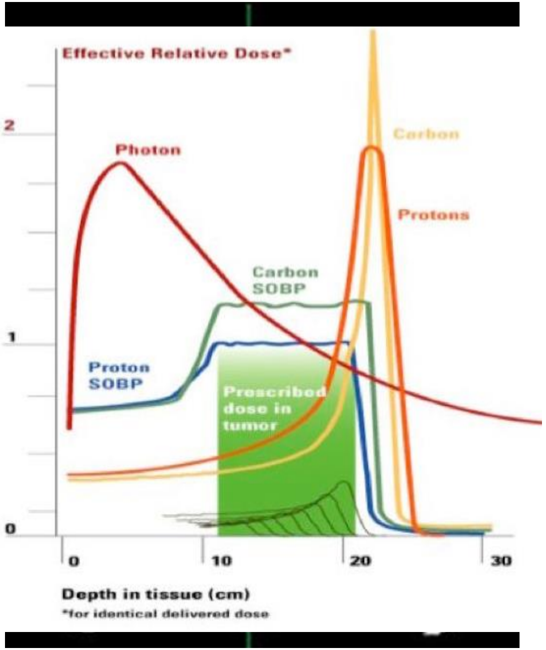
» Solutions
  - ~Proton Imaging with single particle resolution
  - ~Track Structure Imaging
  - ~Ultrafast Beam Monitor

Proton and Ion Therapy have …

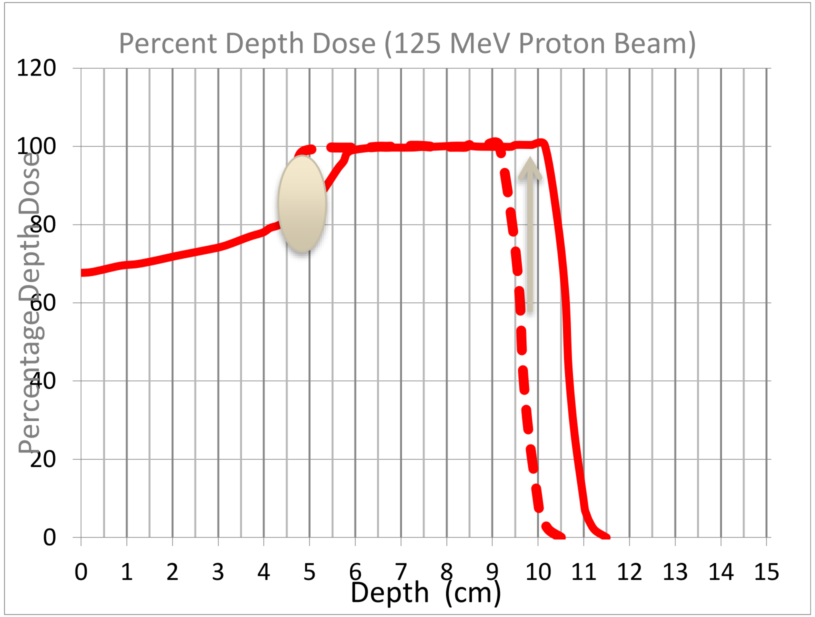
UNSOLVED PROBLEMS

Accepted advantages of proton or ion therapy…

- » Finite range of particle pencil beams
  - ~ High conformality of high dose in irregular macroscopic tumors
  - ~ Possibility of full 3D intensity (fluence) modulate & dose painting
  - ~ Sparing of distal normal tissues (no/minimal exit dose)
  - ~ Distal dose gradient higher than lateral penumbra of photon beams
- » Smaller integral dose in normal tissues
  - ~ Sparing of growing tissues (children)
  - ~ Reduced second cancer induction
  - ~ Less acute side effects during chemo-(particle)-radiation therapy



… results in a problem:



Tumor at 10 cm
sees 100 % of max dose

Patient roll: bone
"appears" at 5 cm depth

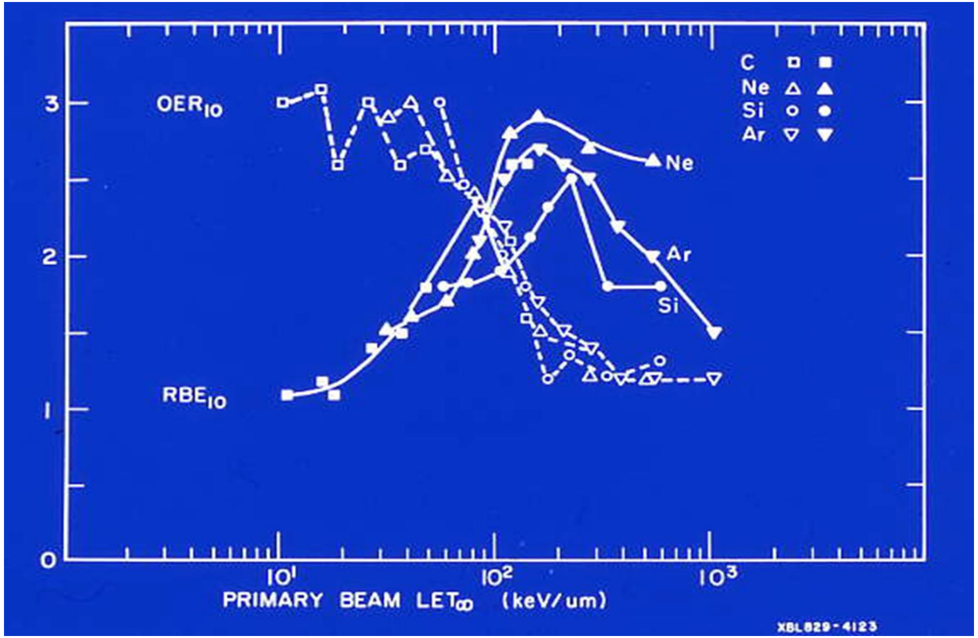
Add 0.5 cm bone
RSP is twice
that of tissue
(0.5cm bone => 1 cm tissue)

Pull back PDD by an
additional 1 cm in tissue

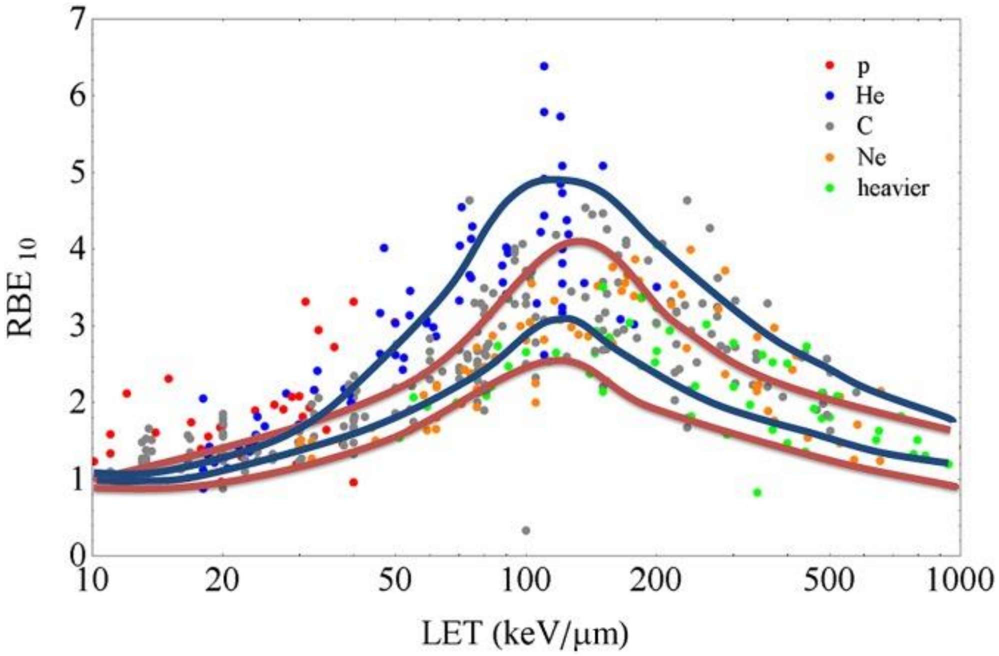
Tumor at 10 cm depth sees ~0% of dose

Biologically enhanced effect of carbon ion therapy (for the same dose)…

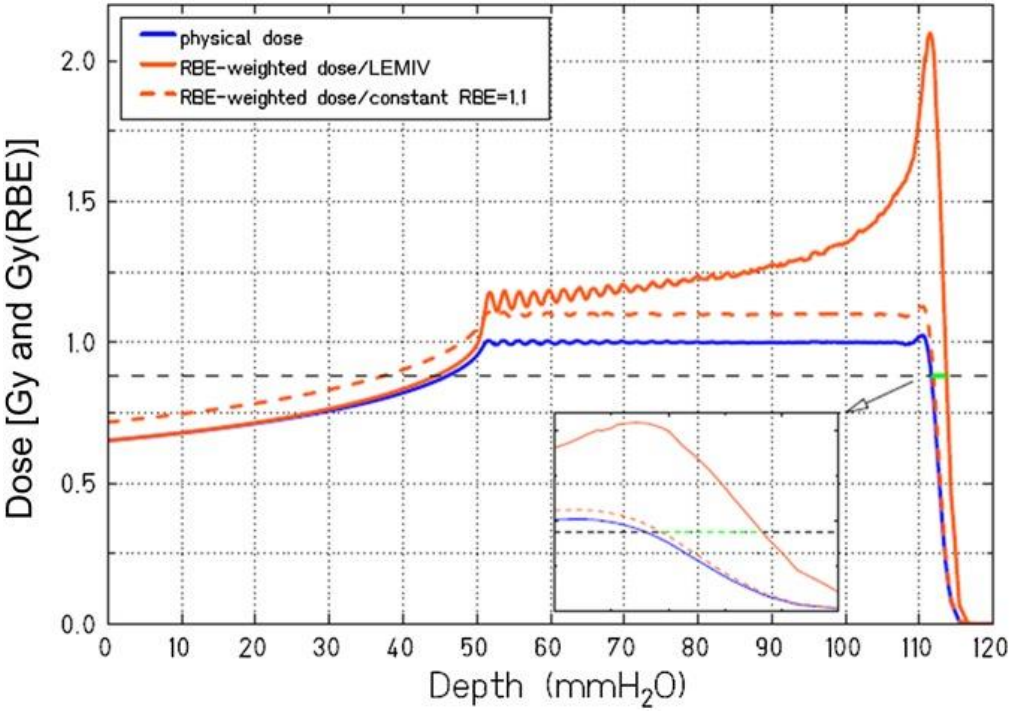
- Bragg peak carbon ions are biologically more effective than protons and ions
  - BED = RBE x physical (high LET) dose
  - Biologically effective dose peaks at around 150 keV/µm (carbon ion SOBP)
- Low LET radiation needs much higher dose for the same biological effect:
  - BED = OER x physical (low LET) dose, OER is typically 2.7-3
  - OER reaches about 1.5 for 150 keV/
  - Less acute side effects during chemo-(particle)-radiation therapy µm (carbon ion SOBP)



… results in higher dosimetric uncertainty



and additional range uncertainty in proton and ion therapy

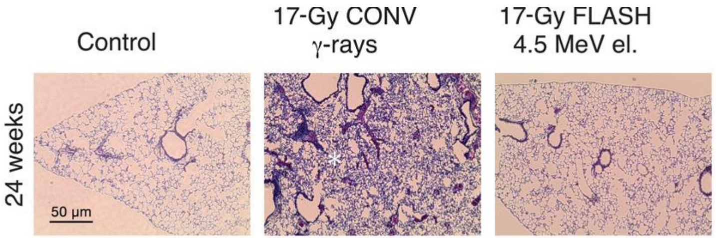


M. Durante, Br J Radiol. March 2014; 87(1035): 20130626.

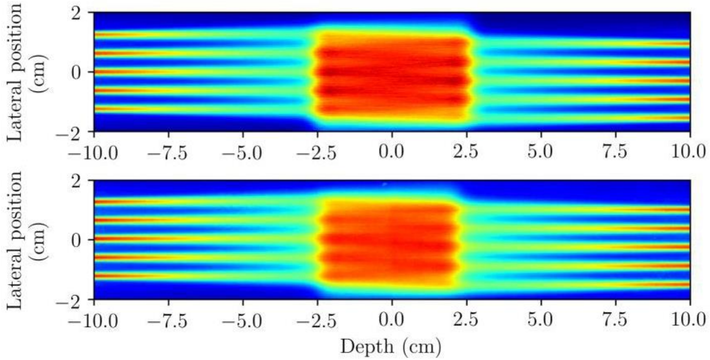
Just around the corner: GRID/Lattice, FLASH & Microbeam Radiation Therapy …

» FLASH effect: A single radiation dose (17 Gy) delivered at ultrahigh dose rate (≥40 Gy/s, FLASH) when compared to conventional dose-rate irradiation (3 cGy/s) creates much less normal tissue damage, but has the same effect on tumor growth in mice. The first clinical trial with proton FLASH is underway.

» GRID effect: large normal tissue sparing to highly spatially fractionated X-ray radiotherapy (GRID/Lattice & MRT) has been explored for many years and is now of interest for proton therapy.



A single dose 17 Gy with electrons spares mouse lung from radiation fibrosis. Favaudon V et al. Sci Transl Med. 2014



Dosimetric verification of proton grid therapy. Freden et al. PTCOG 58, Manchester, UK, 2019.

… demand ultrafast detectors

» Standard ionization chamber dosimetry suffers from recombination effects at dose rates higher than a few Gy/μs, typical for electron FLASH Linac pulses.

» Existing dosimeters are not suitable for large-area monitoring of human FLASH RT fields

» Spatially fractionated RT (GRID/Lattice and MRT) requires spatially resolved dosimetry with sub-millimeter resolution

» Beam monitors need to be redundant, yet non destructive in terms of beam broadening and energy loss.

These problems require …

INNOVATIVE DETECTOR SOLUTIONS

SINGLE PARTICLE IMAGING

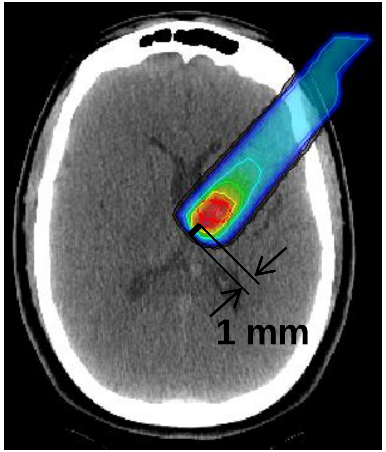
The Use of High-Energy Protons in Cancer Therapy

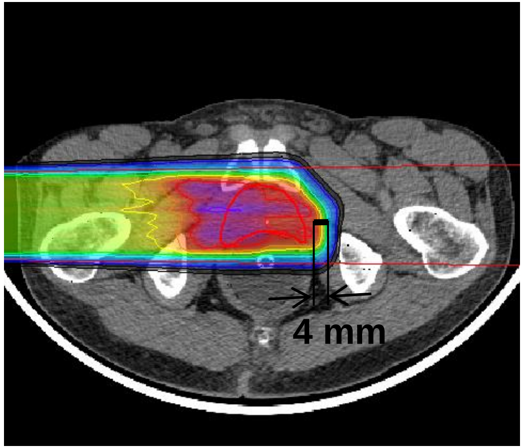
Reinhard W. Schulte
Loma Linda University Medical Center

24. Reuniao de trabalho sobre fisica nuclear no Brasil; Aguas de Lindoia, SP (Brazil); 1-5 Sep 2001

Fundamental X-ray CT Planning Range Uncertainties

- » Two types of uncertainties
  - ~ inaccurate x-ray absorption to RSP conversion
  - ~ beam hardening artifacts
- » Expected range errors

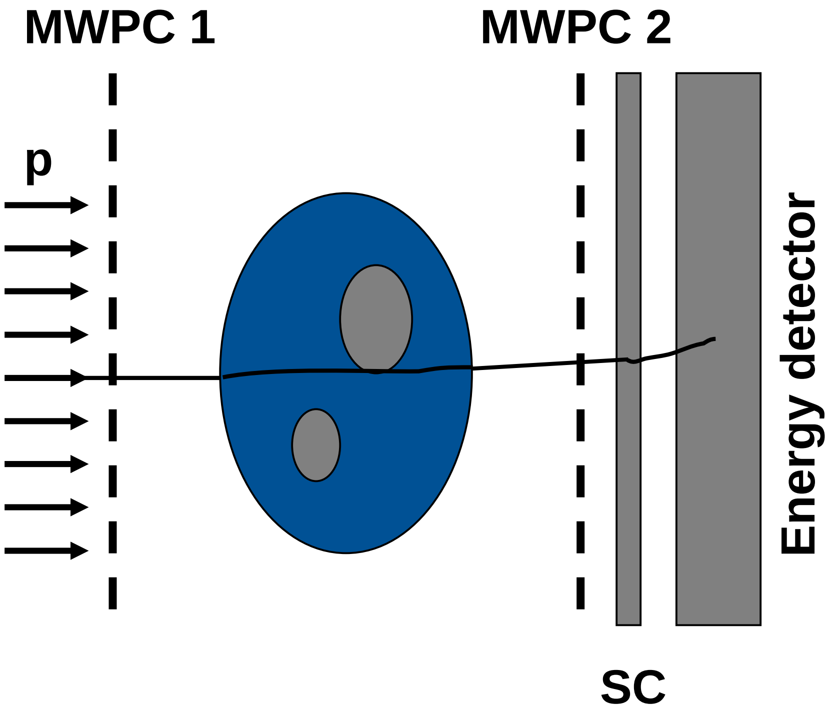




	Soft tissue		Bone	
	H_2O range (cm)	abs. error (mm)	H_2O range (cm)	abs. Error (mm)
Brain	10.3	1.1	1.8	0.3
Pelvis	15.5	1.7	9	1.6

Proton Radiography

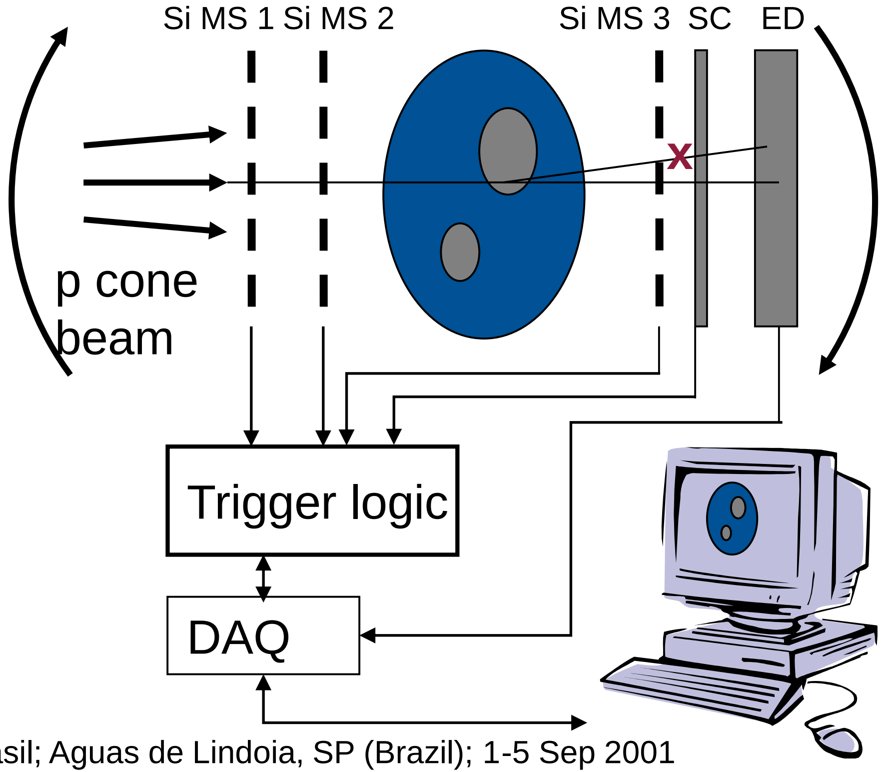
- First suggested by Robert Wilson (1946)
- Images contain residual energy/range information of individual protons
- Resolution limited by multiple Coulomb scattering
- Spatial resolution of 1 mm possible



24. Reuniao de trabalho sobre fisica nuclear no Brasil; Aguas de Lindoia, SP (Brazil); 1-5 Sep 2001

Proton Computed Tomography

» Conceptual design
  - single particle resolution
  - 3D track reconstruction
  - Si microstrip technology
  - cone beam geometry
  - rejection of scattered protons & neutrons



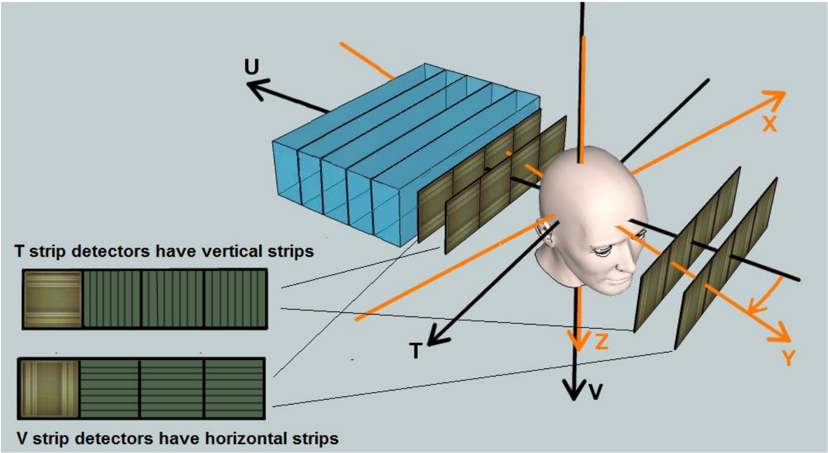
24. Reuniao de trabalho sobre fisica nuclear no Brasil; Aguas de Lindoia, SP (Brazil); 1-5 Sep 2001

U.S. pCT Collaboration (Phase II Scanner)

» The pCT tracker has 8 planes of Si strip detectors: each plane as a T and a V component, measuring 2D coordinates of each proton at a rate of ~1 MHz (up to 1.3 M p per second)

» Each p track is time-correlated to the angle of the rotational platform (not shown), which rotates at ~1 RPM.

» The residual energy of each proton exiting the last tracker plane is measured with a 5-stage plastic scintillator with (PMT) readout. The energy of the 'stopping stage' is converted to WEPL

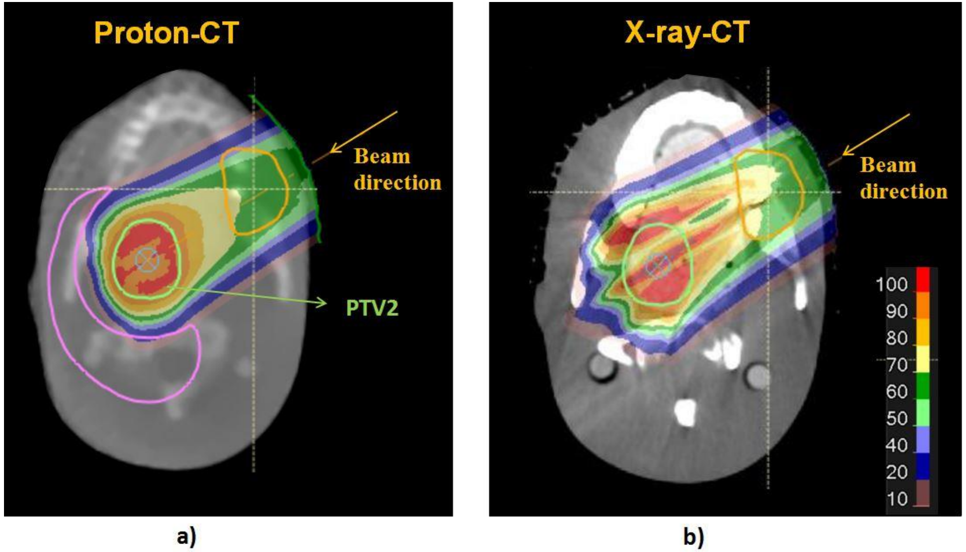


Schematic of the preclinical pCT system with tracking and energy detectors

Robert Johnson, PSD12, Applications of Astro-particle Physics Position Sensitive Detectors Wednesday 11:00 – 11:25

U.S. pCT Collaboration (Phase II Scanner)

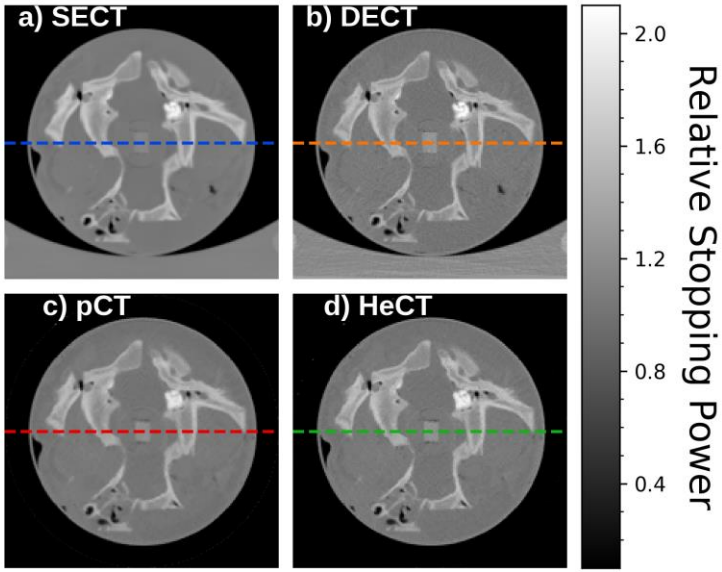
- Proton and ion CT/Rad with single-particle tracking have emerged as promising, yet not clinically implemented, solutions of range uncertainty problems and for online verification
- Early experiments with plastic phantoms show a drastic improvement in planning accuracy in the presence of dental implant artifacts
- More recently experiments have been done with fresh porcine meet samples



Alderson head phantom with dental Ti implant in the beam path planned with proton CT (a) and x-ray CT (b) (C. Oanca et al. 2018 IEEE NSS MIC)

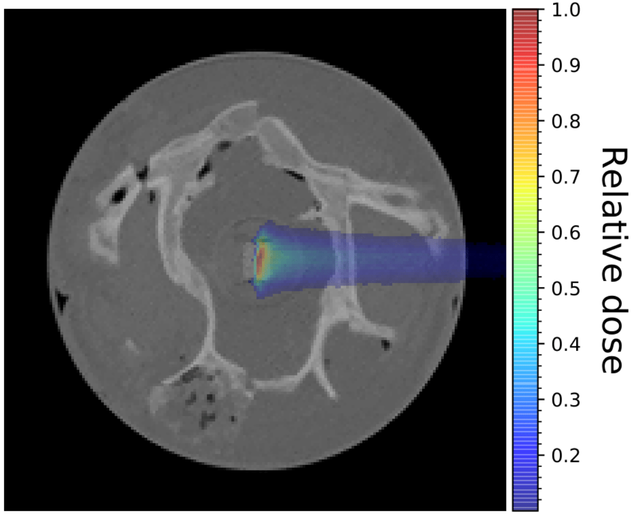
pCT and HeCT with the Phase II Scanner at HIT

- In 2019/2020 a pCT/HeCT measurement campaign took place at the Heidelberg Ion Therapy Center
- A fresh pig head slice was placed in a custom phantom and scanned with conventional single energy xCT (SECT), DECT, pCT, and HeCT
- Range measurement with a proton pencil beam (105 MeV) and 36 EBT-XD films stacked at the center was compared with predicted range using HeCT, pCT, SECT and DECT scans
- A depth-dose GEANT4 simulation based on each modality was used as gold standard

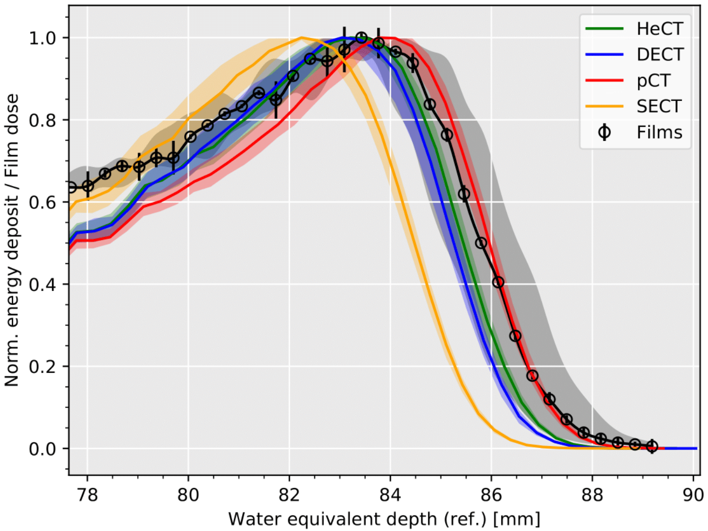


Central slice through the pig head phantom using different modality CT scans ; (L Volz et al., The accuracy of helium ion CT based particle therapy range prediction, 2021, under review by PMB)

Range Accuracy Intercomparison



MC Sim. proton beam dose on HeCT



Comparison of range prediction to film measurement (shaded=uncertainty region)

	SECT	DECT	HeCT	pCT
Relative range accuracy	-1.40±0.24%	-0.45±0.29%	-0.25±0.18%	0.39±0.19%

Courtesy L. Volz, Joint Meeting of the ÖGMP, DGMP and SGSMP, 19-21, Sep, 2021

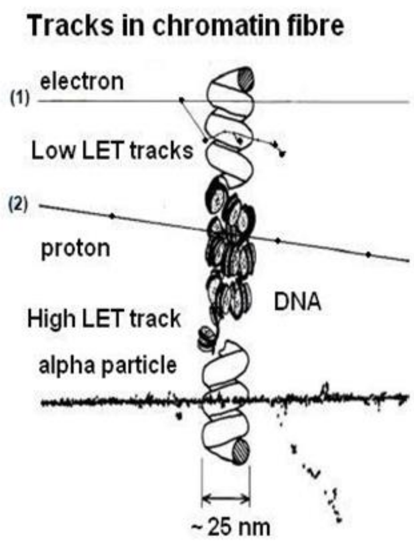
The Future of Image Guidance for Particle Therapy

- Particle tracking for imaging is a promising modality for replacing x-ray imaging for treatment planning and pre-treatment verification.
- Further preclinical studies are needed to show the advantages of range uncertainty reduction in various clinical settings
- Proton radiography is a near-term goal for daily pre-treatment beam's eye view WET checks; single particle tracking may not be necessary if dose/radiograph is not more than ~1 mGy
- Proton CT/HeCT are implementation requires changes to beam intensity (low fluence) and continuous gantry or patient rotation (upright positioning) for image acquisition

COMPACT NANODOSIMETRY

Nanodosimetry: Lessons Learned From Track Structure Simulations

- On the nanometer scale primary ions (incl. protons) form linear tracks, secondary ion tracks (also straight) and tortuous secondary electron tracks
- Low-energy electrons produce ionization clusters on the DNA scale when they stop
- Large ionizations clusters leading to complex DNA damage (simple & complex DSB) are more frequent in high LET radiation



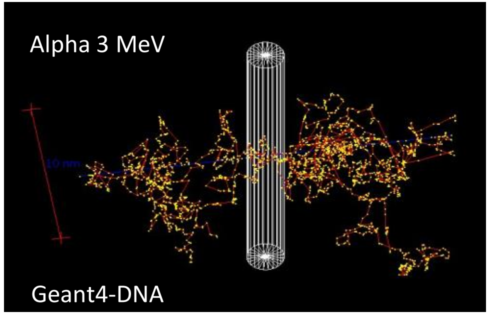
Courtesy D. T. Goodhead

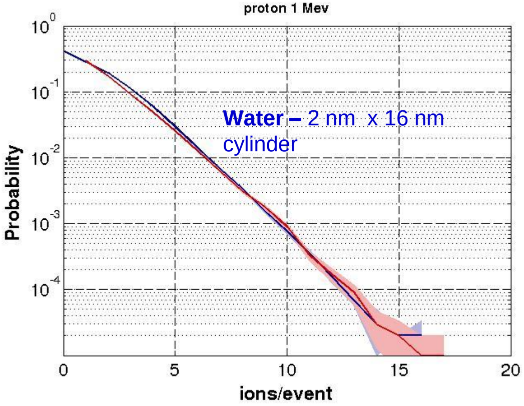
Simulated track entities create ionization clusters of different sizes (v = 1, 2, 3 …) in DNA segments typically limited to 20 bps, <10 nm)

Experimental Nanodosimetry & Track Structure Simulations

- **Ionization cluster size**: number of ionizations produced in a defined target volume of nanometer size (cylinder 2 nm x 10 nm) per primary particle (includes secondaries)
- **Ionization cluster size distribution (ICSD)**: Probability/frequency of event sizes per unit fluence of a mixed radiation field (scales linearly)
- Scaling low-pressure gas to water:

$$D\rho_{gas} = D\rho_{H_2O}\,\frac{\lambda_{gas}}{\lambda_{H_2O}}$$

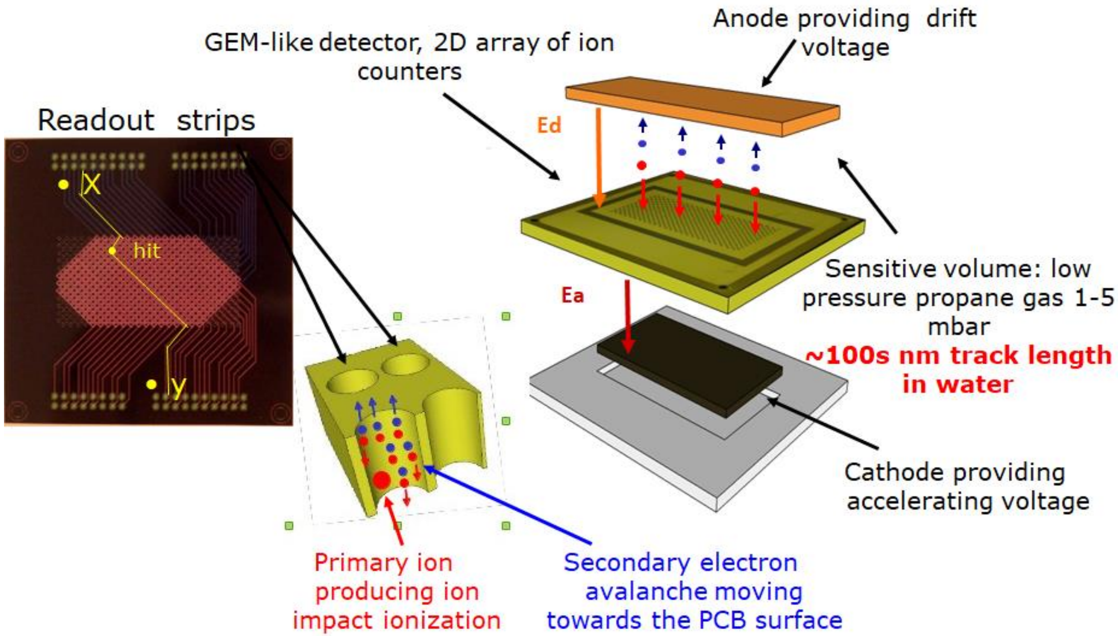




M. Casiraghi, R. Schulte, Treatment plan optimization in particle therapy using nanodosimetric quantities, Rad 2015

Recent ND Detector Developments (2009-2020)

- A new concept of a concept of a gas-based position sensitive detector has been developed at LLU since 2009 (lead Vladimir Bashkirov, PhD)
- The detector drives track generated gas ions in low-pressure gas (propane or water vapor) into a hole pattern with high electric field creating a limited gas multiplication



Fabiano Vasi, Development and Characterization of a Compact Gaseous Nanodosimeter for Radiotherapy, Doctoral Dissertation, Zurich University, 2020
Margherita Casiraghi, Nanodosimetric Track Structure Studies for Applications in Particle Therapy, Doctoral Dissertation, 20217 ETH Zurich,

A new Paradigm: Equal ND Clustering = Equal Biological Effect for the Same Biological System

» Rather than using absorbed dose or LET (the average amount of energy transferred per unit mass or track length), one should focus on the number of disruptive events (ionizations) occurring on the nanometer (DNA) scale.

» Tumor: A tumor of a given type will be controlled if the amount of small ionization clusters exceeds a certain amount. Additional large clusters (rare with low LET, but common with high LET) will add to the biological effectiveness and improve tumor control

» Normal Tissues: Late normal toxicity is related to the number of large clusters either in a small volume (serial tissues) or the entire volume of an organ at risk (parallel tissue). If one stays below the threshold for large clusters (known from low LET tolerance dose) no toxicity should be observed.

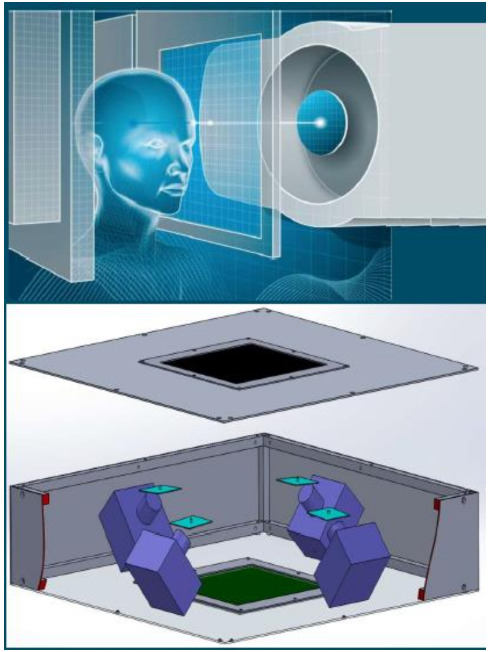
The Future of Hadron Therapy Planning

- Nanodosimetry-based planning could replace LET- or RBE-based planning
- A new system of metrology for measuring number ionizations in nanometer equivalent volumes (array of small nanodosimeters) would be needed (under development)
- Calculation of ionization cluster size distributions on a voxel-by-voxel bases using MC track structure simulations is computationally feasible (demonstrated)
- New treatment plan optimization/feasibility seeking will be based on ICSD parameter constraints, not dose constraints
- Much radiobiological validation work remains to be done

FLASH RT BEAM MONITOR

Ultrafast & Precise Beam Monitor for FLASH and non-FLASH Radiation Therapy

- A modular beam monitor that can either be attached to existing or integrated into new beamlines for FLASH RT has been developed and tested
- Array of fast cameras operating at readout/analysis speeds of ~ 10 kHz
- fast readout and low mass (< 0.5 mm WET) technology will enable clinical trials of FLASH



Peter Friedman, PSD12, Novel Thin-Scintillator Ion Beam Imagers, Poster Session 5, Thursday 10:30

Take Home Points

- Modern radiation therapy has many potentials (lower dose, better dose control, higher biological effectiveness against resistant tumors) for better cancer patient outcomes (increased cure rates, lower toxicity)
- Radiation detectors with high position and time resolution are at the interface between physics and radiation therapy
- Physicists/engineers need to be trained to work together to allow faster translation

Acknowledgement

- The list of collaborators, institutions, small businesses, and consortia has grown too long to be mentioned on one slide
- I am looking forward to meeting old and new friends again in person in the near future

Friends of Reinhard meet at PTCOG Manchester, 2019

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