Proton CT
A novel diagnostic tool in cancer therapy

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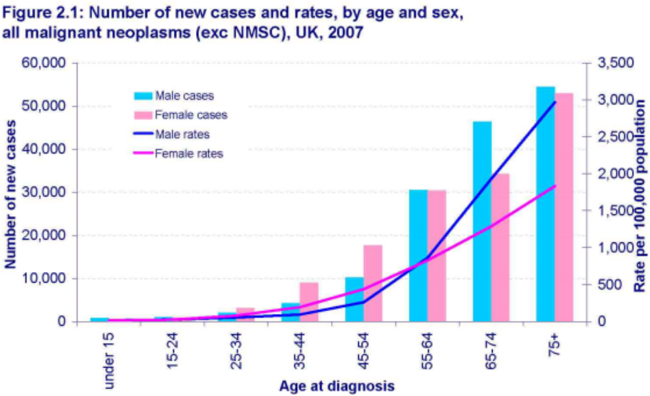
MTA Wigner RCP

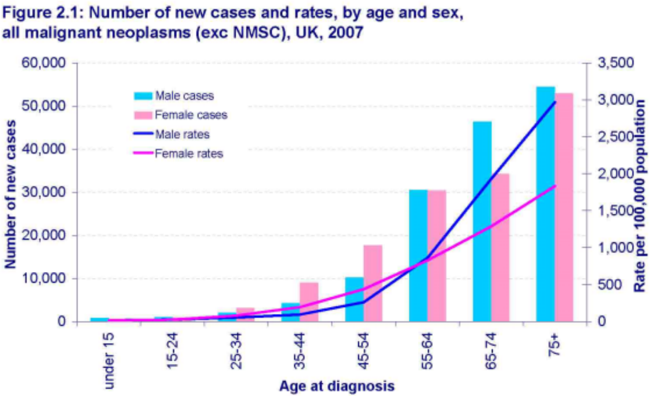
7th September 2018

HEPHY Seminar

Cancer statistics and therapies



Cancer statistics and therapies



- Contributions to successful treatment of cancer
  - 45-50% surgery
  - 40-50% radiotherapy
  - 10-15% chemotherapy
- Radiotherapy is an important weapon in the battle against cancer

K. Peach, Heavy Ions in Science and Health workshop, Bergen, 2012

Radiotherapy and its problems

- Goal: damage the DNA of cancer cells
- Direct or indirect ionization
- Treatment with photons or charged particles (e.g. protons)
- Photons: mostly indirect ionization through forming free radicals
- Protons: mostly direct ionization

Radiotherapy and its problems

- Goal: damage the DNA of cancer cells
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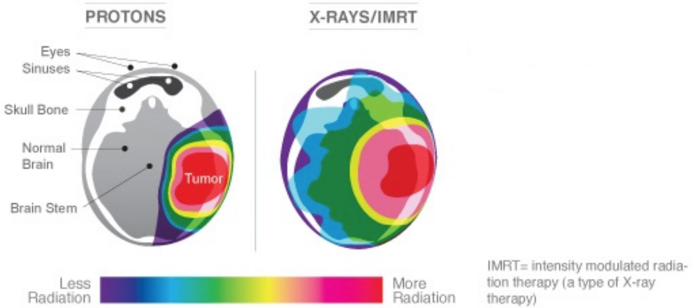
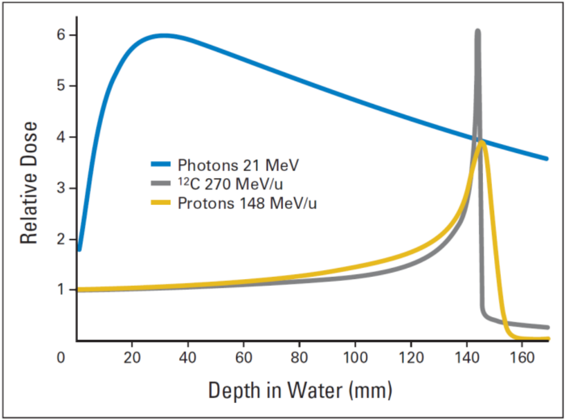
- Treatment with photons or charged particles (e.g. protons)
- Photons: mostly indirect ionization through forming free radicals
- Protons: mostly direct ionization
- Need to minimize the damage to healthy tissue



Source: ProCure Training and Development Center

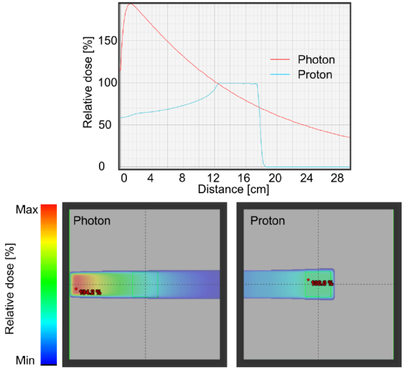
Hadron therapy – advantages



- **Photons** are absorbed mostly at the entrance
- **Charged particles**
  - lose most of their energy in the Bragg peak
  - Relatively low dose in front of the tumor
  - Sharp fall-off of dose deposition (<mm)

Hadron therapy – advantages

- Irradiate from one or four angles
- Relative dose to healthy tissues is much more in the case of photons



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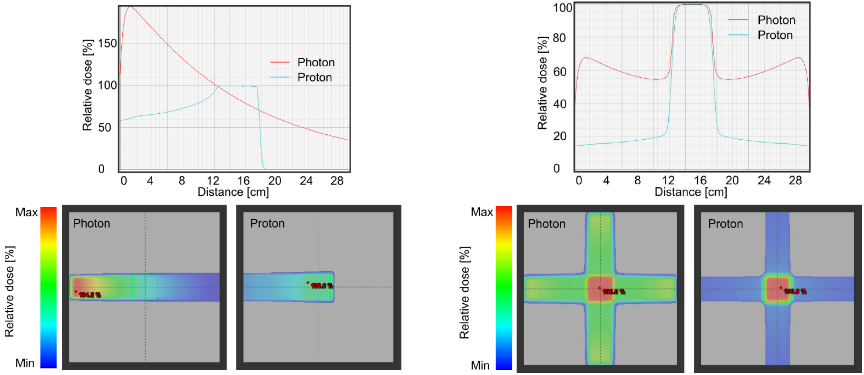

Irradiation choices

	Photons	Protons	Carbon ions
Integral out-of-field dose	1	0.3 – 0.5	< 0.3
Relative Biological Effectiveness	1	1.1	> 3 in Bragg peak

- Integral out-of-field dose: the smaller the better (ideally 0)
- Relative Biological Effectiveness: the higher the better
- Qualitative difference between photons and carbon-ions

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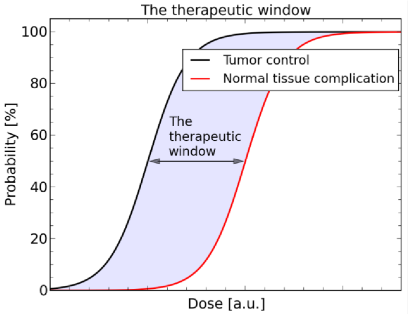
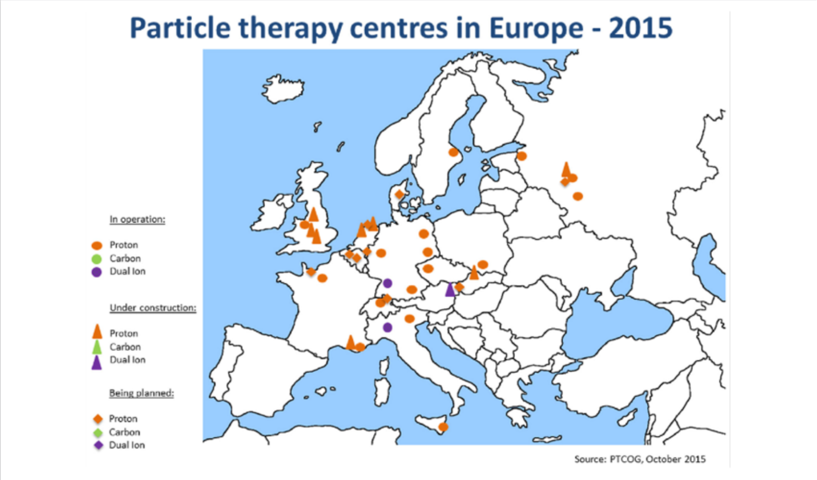


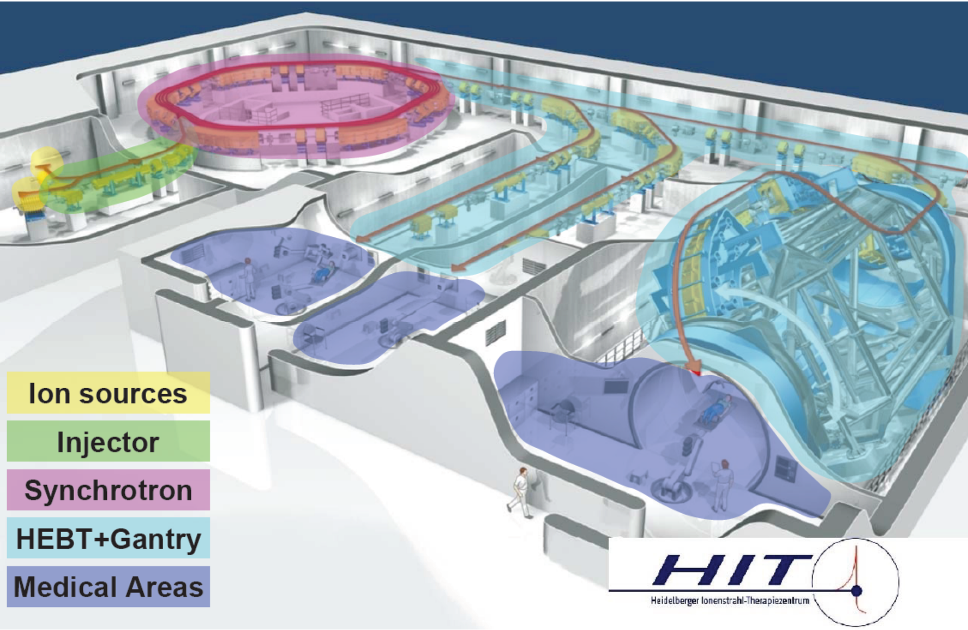
Hadron therapy centers in Europe



- Three C-ion centers
- 27 proton centers

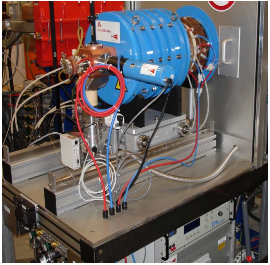
M. Dosanjh, M. Cirilli, S. Myers, S. Navin (2016). Medical applications at CERN and the ENLIGHT network. Frontiers in Oncology. 6. 10.3389/fonc.2016.00009.

Treatment facilities

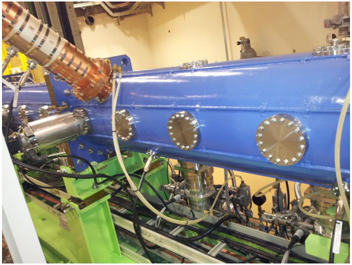


Treatment facility

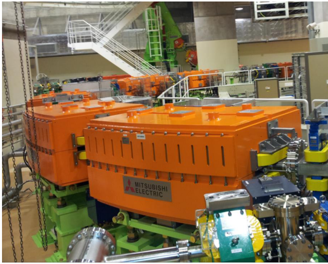
Ion source



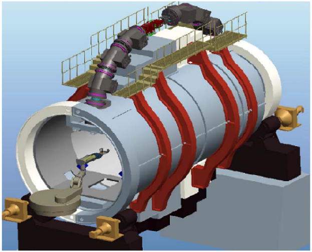
LINAC



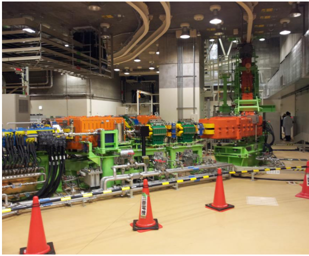
Synchrotron



Treatment room



Superconducting gantry



Extraction and beam transport

A typical ion facility in 2014

- Beam species
  - light ions (e.g. C)
  - protons
- Beam energies
  - Therapeutic beam: range in water: $33 - 38$ cm
    $\longrightarrow$ carbon ion (6+): $80 - 450$ MeV/nucleon
    $\longrightarrow$ proton: $40 - 250$ MeV
  - Diagnostic beam: relativistic proton beam: 800 MeV
- Energy resolution: $\Delta E/E \sim 0.2\%$
- Beam quality
  - Pencil beam $\rightarrow$ 3D voxels spot size few mm
  - ~ 1 mm Bragg peak width
- $\sim 1 - 2$ min per treatment field

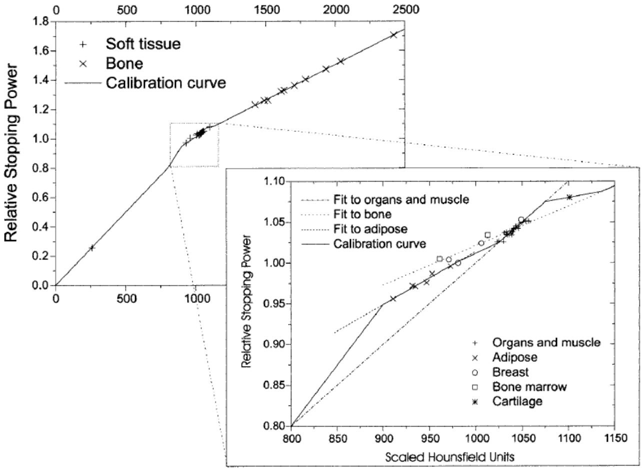
Proton therapy – missing information

- Stopping power in front of the tumor to be known precisely
- Stopping power is described by Bethe-Bloch formula:

  $$dE/dx \sim \text{electron density} \times \ln \frac{\text{max. energy transfer in single collision}}{\text{effective ionization potential}^2}$$

- Derive stopping power from X-ray CT
- X-ray attenuation in tissue depends also strongly on Z (Z^5 for photoelectric effect)

Proton therapy – missing information



- Scaled Hounsfield Units $\sim$ attenuation coefficient
- Not a clear relation with the stopping power

Schaffner, B. and E. Pedroni, The precision of proton range calculations in proton radiotherapy treatment planning: experimental verification of the relation between CT-HU and proton stopping power. Phys Med Biol, 1998. 43(6): p. 1579-92.

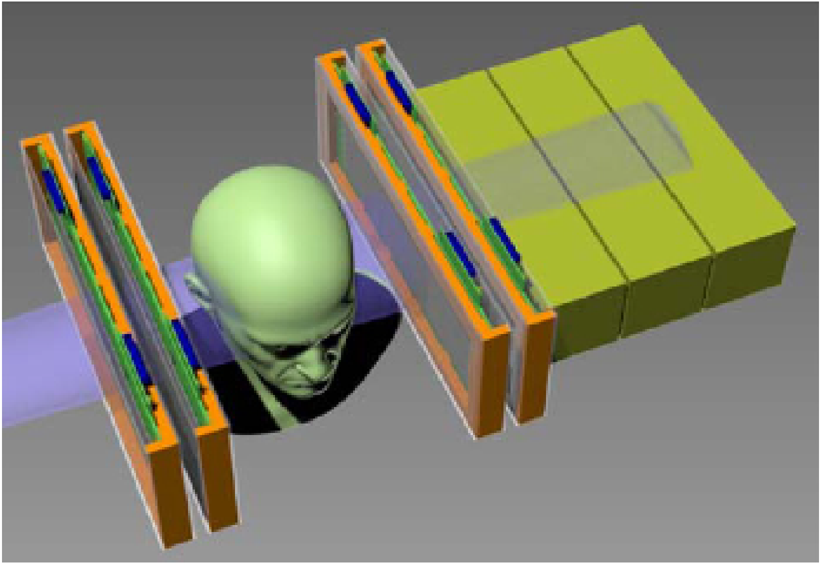
Range uncertainties

- Single energy CT: up to 7.4% uncertainty
- Target volume is increased by up to 1 cm in beam direction
- Avoid beam directions with a critical organ behind the tumor
- Dual energy CT: up to 1.7% uncertainty
- Proton CT: up to 0.3% uncertainty

A comparison of dual energy CT and proton CT for stopping power estimation

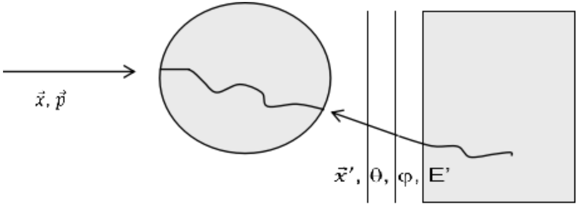
David C. Hansen,[1, a)] Joao Seco,[2] Thomas Sangild Sørensenn,[3] Jørgen Breede Baltzer Petersen,[4] Joachim E. Wildberger,[5] Frank Verhaegen,[6] and Guillaume Landry[7]
[1)] *Department of Experimental Clinical Oncology, Aarhus University*

Proton CT – concept



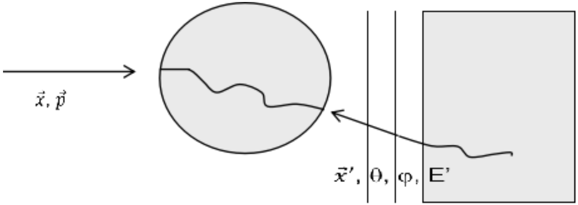
H.F.-W. Sadrozinski / Nuclear Instruments and Methods in Physics Research A 732 (2013) 34–39

Proton CT – concept



- $\vec{x}$ and $\vec{p}$ from beam optics and scanning system
- $\vec{x'}$, θ, φ and E' to be measured

Proton CT – concept



- $\overrightarrow{x}$ and $\overrightarrow{p}$ from beam optics and scanning system
- $\overrightarrow{x'}$, θ, φ and E' to be measured

- Reconstruction of trajectories in 3D $\longrightarrow$ place of irradiation
- Measurement of range in external absorber $\longrightarrow$ lost energy

- Before the treatment $\longrightarrow$ 3D map of electron density in target
- Quasi-simultaneously with therapeutic beam $\rightarrow$ online verification of dose

Proton CT – images

- Transmission map
  - Records loss of protons
  - Nuclear reactions
- Scattering map
  - Records scattering of protons
  - Coulomb potential
- Energy loss map
  - Records energy loss of protons
  - Bethe-Bloch

Cecile Bopp. PhD thesis, Strassbourg, 2013

Requirements of the detector

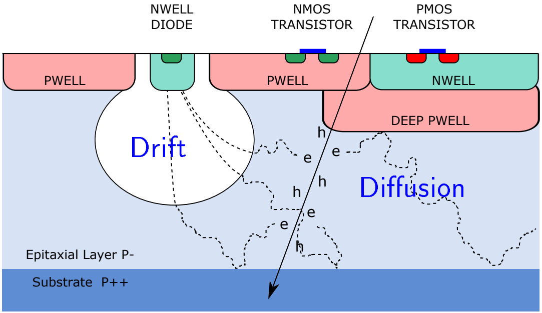
- High position resolution (tens of μm)
- Simultaneous tracking of large particle multiplicities ($10^7 - 10^9$ protons/s)
- Fast readout
- Radiation hardness
- Front detector: low mass, thin sensors ($50 - 100\ \ \mu$m)
- Back detector: good range resolution

$$\Downarrow$$

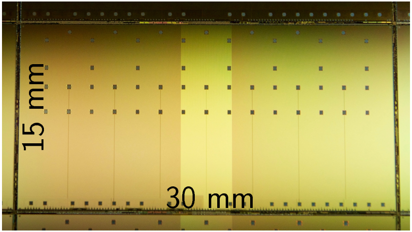
- High granularity digital sampling calorimeter
- Monolithic Active Pixel Sensors (MAPS) as active layers

Monolithic Active Pixel Sensors (MAPS)

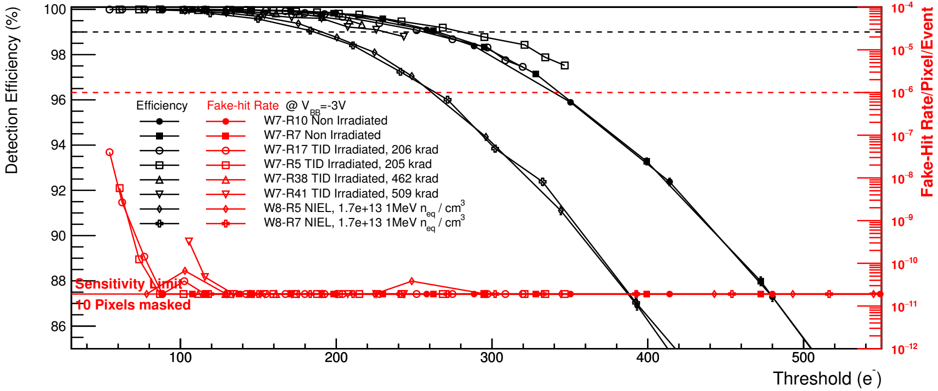
- Silicon sensors
- Using TowerJazz 0.18 μm CMOS imaging process
- High-resistivity ($> 1\text{k}\Omega$ cm) epitaxial layer on p-type substrate
- Deep PWELL shields NWELL of PMOS transistors
  - Allows full CMOS circuitry in active area
- Moderate reverse substrate biasing possible
  - Larger depletion volume



- ALPIDE – **AL**ICE **PI**xel **DE**tector
- Developed for the upgrade of the ALICE Inner Tacker System
- Large silicon sensor (15 mm $\times$ 30 mm)
- 512 $\times$ 1024 pixels
- Pixels are 27 µm $\times$ 29 µm
- Digital readout with priority encoder
- Thin sensor (50 µm or 100 µm)
- Efficiency $>$ 99%
- Resolution $\sim$ 5 µm

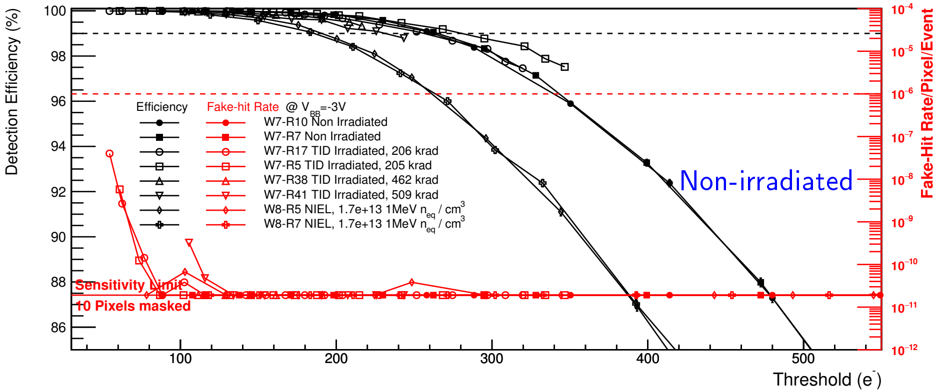


Efficiency and fake hit rate



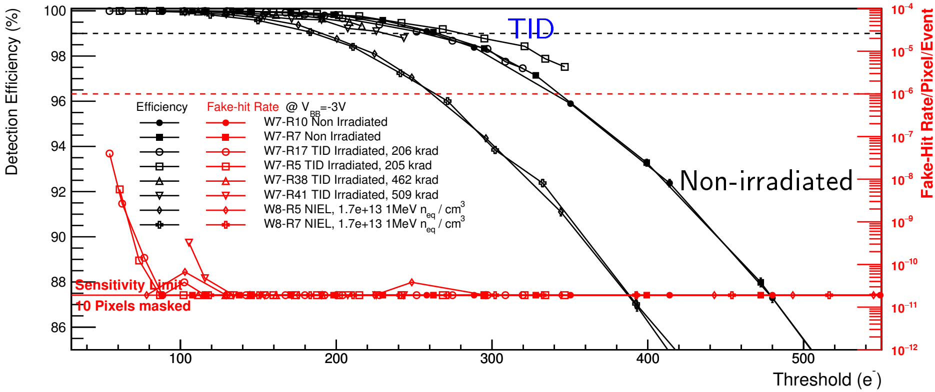
- Fake hit rate is below sensitivity for most measurements

Efficiency and fake hit rate



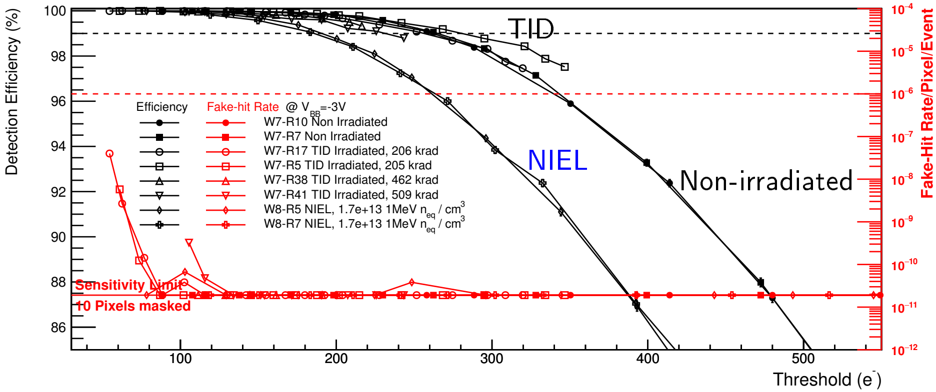
- Fake hit rate is below sensitivity for most measurements
- Efficiency is above 99% below 220 electrons

Efficiency and fake hit rate

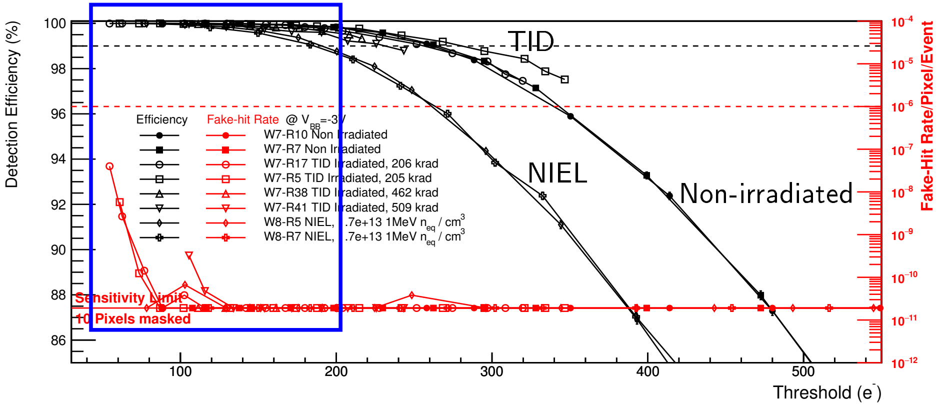


- Fake hit rate is below sensitivity for most measurements
- Efficiency is above 99% below 220 electrons
- No degradation from TID

Efficiency and fake hit rate

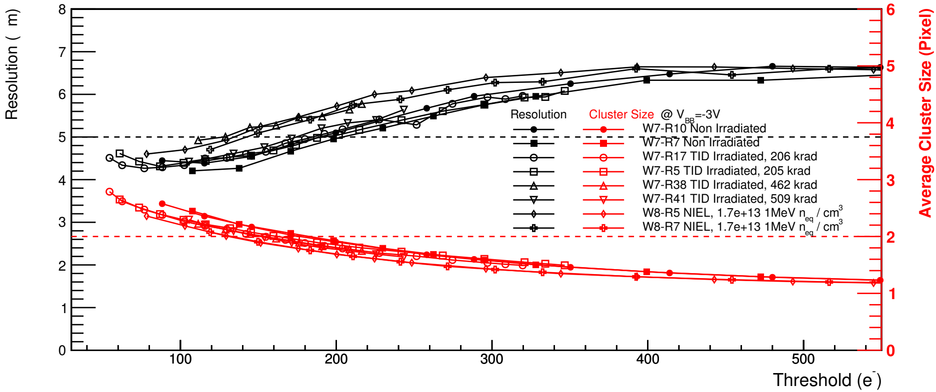


- Fake hit rate is below sensitivity for most measurements
- Efficiency is above 99% below 220 electrons
- No degradation from TID
- Small degradation from NIEL



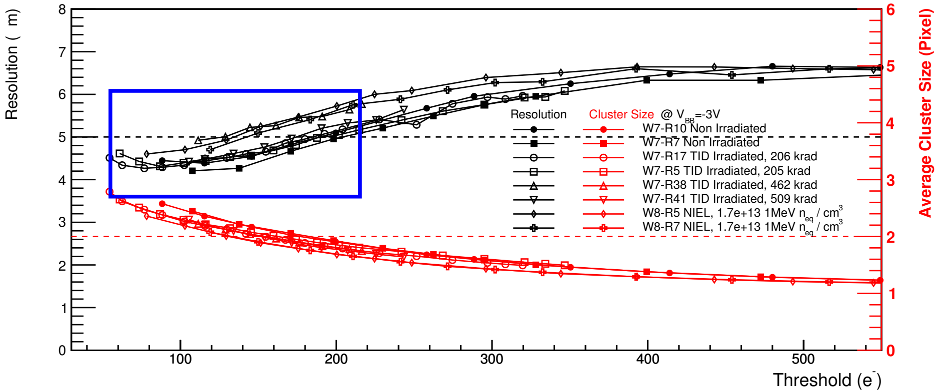
- Fake hit rate is below sensitivity for most measurements
- Efficiency is above 99% below 220 electrons
- No degradation from TID
- Small degradation from NIEL
- Large operational margin after irradiation

Resolution and cluster size



- Cluster size is around 2

Resolution and cluster size



- Cluster size is around 2
- Resolution below 5 µm below 200 electrons

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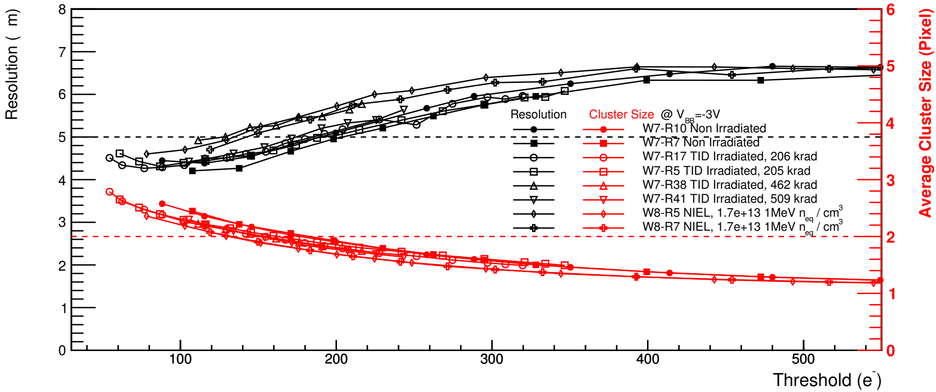
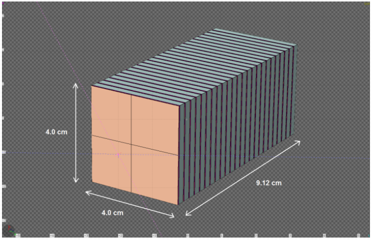
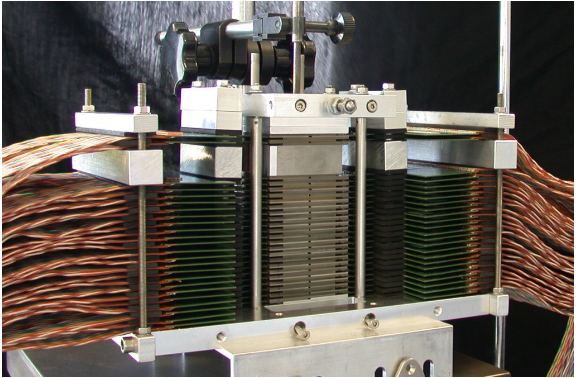


- Cluster size is around 2
- Resolution below 5 μm below 200 electrons
- No degradation from TID or NIEL
- Operational margin doesn't change after irradiation

Digital calorimeter prototypes

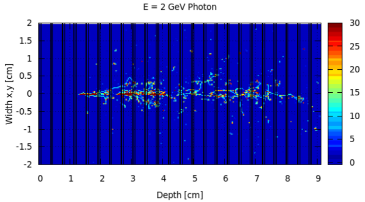
- Silicon-tungsten sampling calorimeter
- Optimized for electromagnetic showers
- Active layers: MAPS (MIMOSA 23 – IPHC Strasbourg)
- Compact design $4 \times 4 \times 11.6$ cm^3
- 24 layers
- Absorbers: 3.5 mm of W



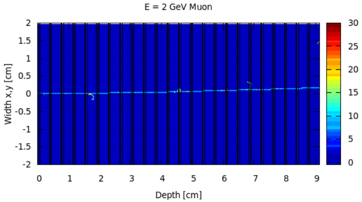


Simulations results

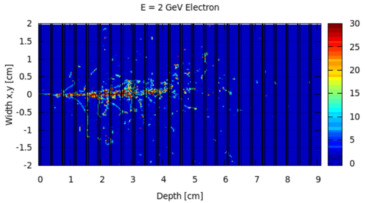
Photons



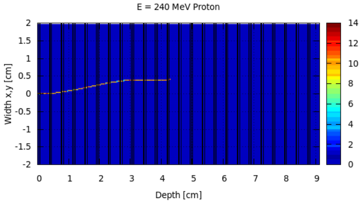
Muons (MIP)



Electrons



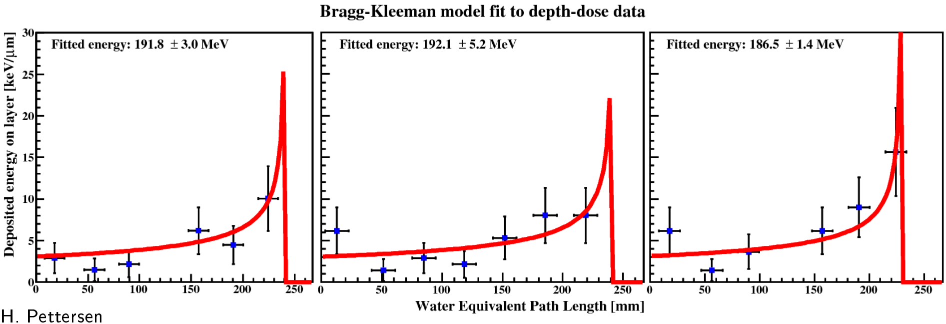
Protons



Results from the prototype

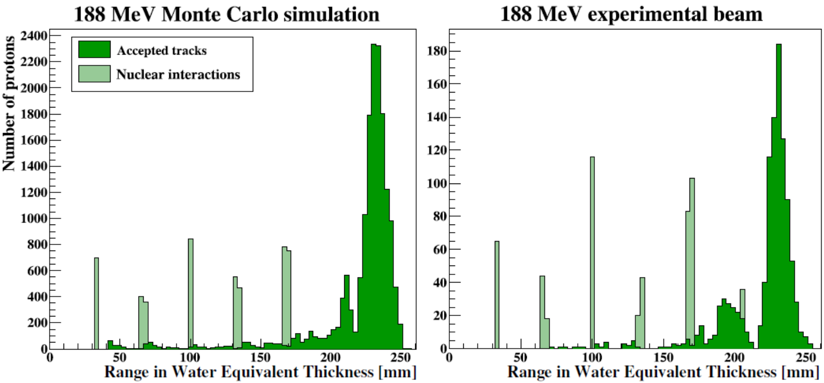
- Tracking of a single proton
- Collecting clusters along the trajectory
- Fitting a Bragg curve

Bortfeld, T. An Analytical approximation to the Bragg curve for therapeutic proton beams. Med. Phys 24 2024-33 (1997)



H. Pettersen

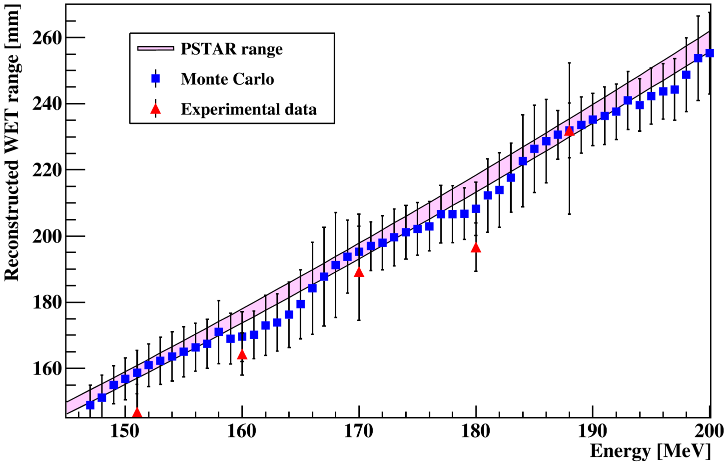
Results from the prototype



H. Pettersen, PhD thesis, UiB, 2018

- Good agreement between data and simulations

Results from the prototype



H. Pettersen, PhD thesis, UiB, 2018

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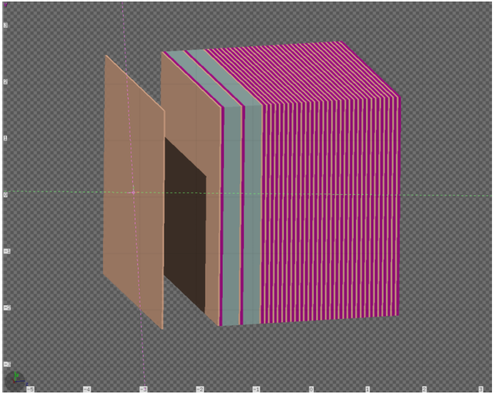
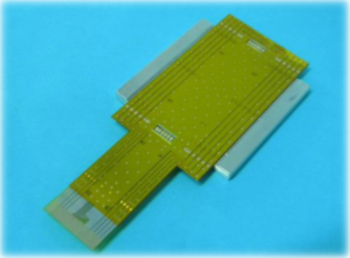
Optimization of the design

- Geometry
  - Front area: 27 cm x 15 cm
- Longitudinal segmentation
  - Number of sensitive and absorber layers: 41
- Absorber
  - Energy degrader, mechanical carrier, cooling medium
  - Material choice: Al
  - Thickness (3.5 mm)



Mounting

- ALPIDE mounted on thin flex cables
  - Aluminum-polyamide dielectrics: 30 μm Al, 20 μm plastic
  - Design and production: LTU, Kharkiv, Ukraine
- Intermediate prototype
  - Chip cable with two ALPIDE sensors



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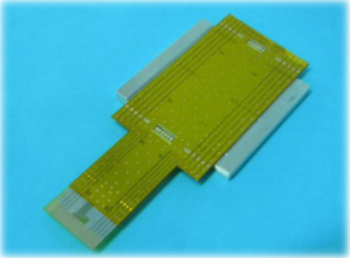
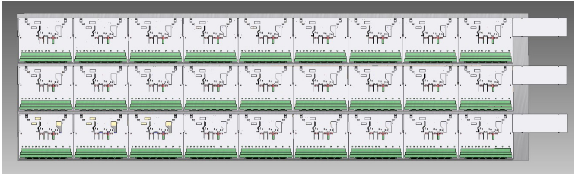
  - Chip cable with two ALPIDE sensors
- Final system
  - Flexible carrier board modules with 2×3 strings with 9 chips





Group

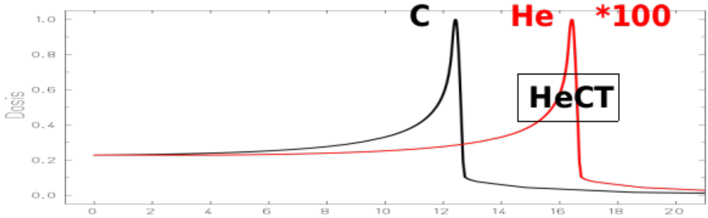
- Organization
  - University of Bergen
  - Bergen University College
  - Helse Bergen
  - Utrecht University
  - DKFZ Heidelberg
  - Wigner Budapest

- Financing
  - 44 million NOK ($\sim$ 4.5 million EUR), 5 years (2017-2021)

Norwegian government has decided to build two particle therapy facilities (Oslo, Bergen), to be operational by 2022

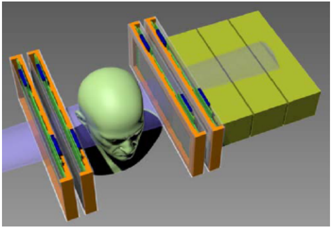
Next steps

- Finishing the optimization of the design
- Construction of prototype
  - First chip cables with mounted chips are being tested
  - First sensor module: December
- Start mass production of ALPIDE chips
- Extensive commissioning with proton beams
- Commissioning with He beams
  - HeCT – less multiple scattering, better resolution
    PhD thesis C. Collins Fekete, Univ. Laval, 2017
  - Carbon beam with 1% Helium (as proposed by GSI/HIT and CNAO)



Conclusions

- Hadron therapy $\longrightarrow$ lower unnecessary dose for the patient
- Uncertainty in energy loss from extrapolation from CT
- pCT: novel diagnostic tool to reduce the uncertainty
- Digital sampling calorimeter made of ALPIDE sensors
- First sensor module by the end of the year



Thank you for your attention!

BACKUP