Prompt-gamma radiation in proton therapy – activities of the SiFi-CC collaboration

Aleksandra Wrońska
Jagiellonian University in Cracow
SiFi-CC group
https://bragg.if.uj.edu.pl/sificc

Seminar @ University of Warsaw, 27.10.2022

Cancer – a scare and a challenge

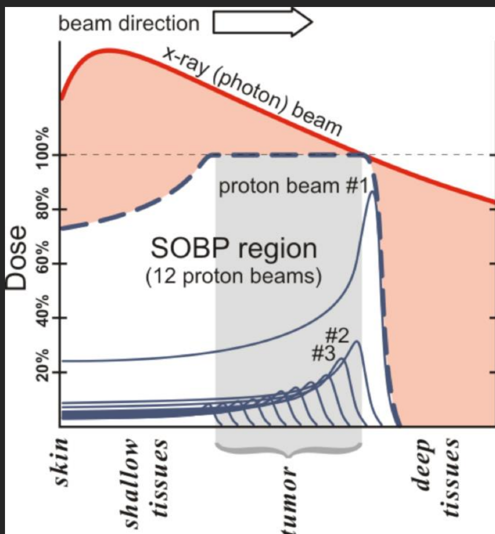
Statistics

- 1 in 4 deaths caused by cancer in the EU
- (Poland close to this average)
- responsible for more than 35% of deaths among those aged less than 65, and under 25% amongst those aged 65 and over
- >3.7 million new cases and ~1.9 million deaths/year make cancer the second most important cause of death and morbidity in Europe
- main causes: tobacco and alcohol consumption, inappropriate diet, obesity and insufficient physical activity, longer life
- trend: increasing...

Treatment methods

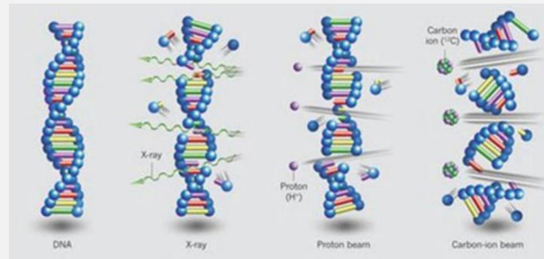
- Surgery
- Chemotherapy
- Radiotherapy
- Immunotherapy (Nobel prize 2018)

X-ray vs hadron therapy

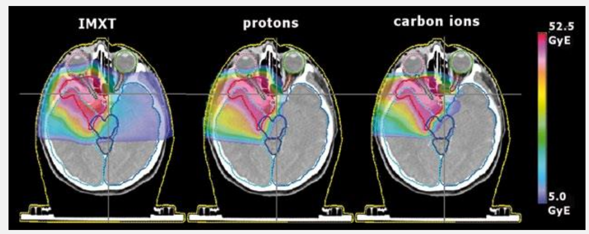


Levin et al.., British J of Cancer 2005

- Tumour irradiation – an important way of treatment
- Advantages of hadron therapy compared to X-rays:
  - Conformal dose distribution
  - Biological effectiveness



Marcos dAvila Nunes, Springer 2015



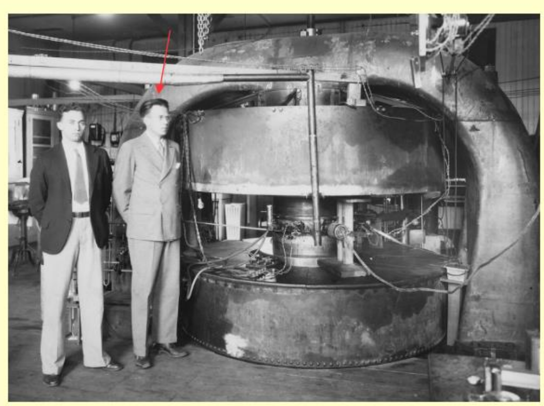
NuPECC, Nuclear Physics for Medicine 2014

PT - history

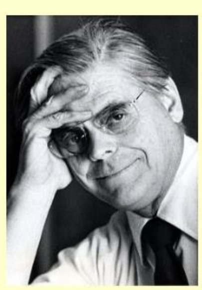
Hans Bethe 1930: interaction of hadrons with matter

$$-\left\langle \frac{dE}{dx} \right\rangle = \frac{4\pi}{m_e c^2} \cdot \frac{nz^2}{\beta^2} \cdot \left(\frac{e^2}{4\pi\varepsilon_0}\right)^2 \cdot \left[\ln\left(\frac{2m_e c^2 \beta^2}{I \cdot (1-\beta^2)}\right) - \beta^2\right]$$

Ernest O. Lawrence 1932: construction of cyclotron



Robert Wilson 1946: use of proton beams for cancer therapy



Developments in hadron therapy

- First patient irratiation 1954 at Berkeley (2 years after tests with mice)
- Subsequent improvements:
  - utilization of Bragg peak
  - tests with other ion species
  - fractionated delivery
  - utilization of spread-out Bragg peak (ripple filters)
  - technology transfer from research institutes to hospitals
  - commercial companies enter the field
  - modern CT+PET assisted evaluation of treatment plans based on sophisticated computer simulations
  - multi-field irradiations, scanning with pencil beam
  - >100 therapy centres operational, and counting...

PRECISE AND SELECTIVE TREATMENT

Need for beam range monitoring

- Steep slope of dose distribution – benefit / issue
- Tumours close to critical organs (spinal cord, brain structures) need precision in dose delivery
- Clinical practice: range uncertainties → need to compromise dose conformality and safety
- „ In-vivo range verification methods would represent an optimal solution for full explotitation of the advantages afforded by the ion beam”
  - Reduction of safety margins, better treatment plans
  - Potential to treat new patients categories

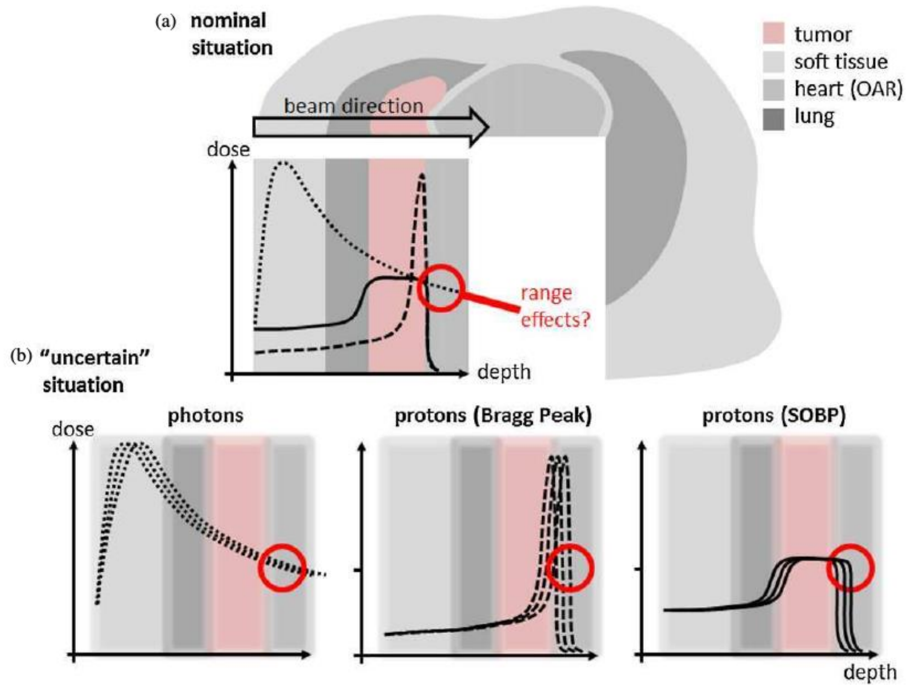
NuPECC, Nuclear Physics for Medicine 2014

Table 4. Uncertainty in range [Paganetti 2012].

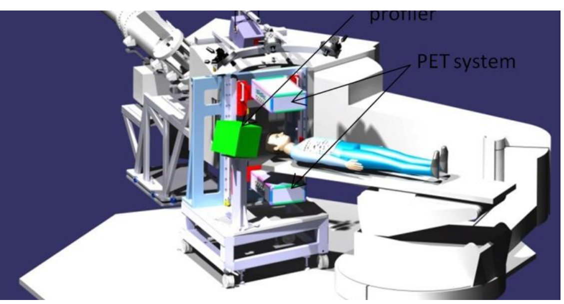
Source of range uncertainty in the patient	Range uncertainty
Independent of dose calculation:	
Measurement uncertainty in water for commissioning	± 0.3 mm
Compensator design	± 0.2 mm
Beam reproducibility	± 0.2 mm
Patient set up	± 0.7 mm
Dose calculation:	
Biology (always positive)	+ 0.8%
CT imaging and calibration	± 0.5%
CT conversion to tissue (excluding I-values)	± 0.5%
CT grid size	± 0.3%
Mean excitation energies (I-values) in tissue	± 1.5%
Range degradation; complex inhomogeneities	- 0.7%
Range degradation; local lateral inhomogeneities*	± 2.5%
Total (excluding *)	**2.7% + 1.2 mm**
Total	**4.6% + 1.2 mm**

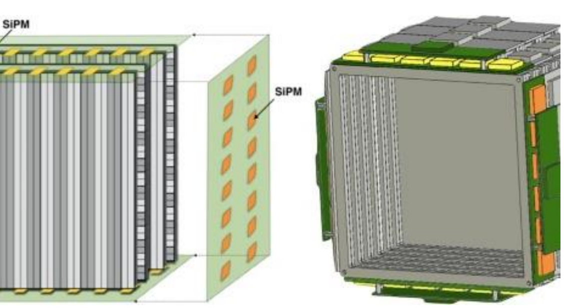
Can we do better in proton therapy?

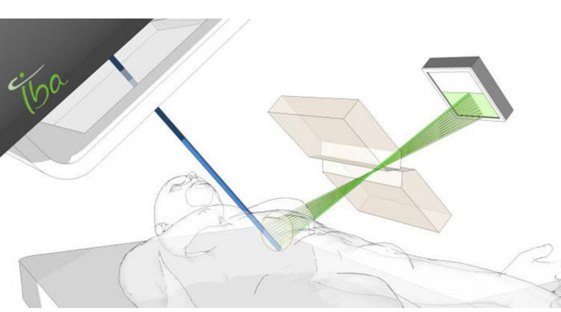
- Safety margins: from a few mm up to > 1 cm
  - Patient positioning
  - Anatomical changes
  - Infections
  - Uncertainties of treatment planning
- Reduction of margins?
- Online monitoring of therapy
  - Determination of Bragg peak position in real time, spot-by-spot
  - Maybe even spatial dose distribution...?



Knopf, Lomax, PMB 2013







How to monitor PT?

Secondary radiation

- Protons, neutrons - useful in C-ion therapy:
  - Dose Profiler (CNAO) Traini *et al.*, Physica Medica 65, 2019
  - MONDO (CNAO) Mirabelli *et al.*, *IEEE Trans. Nucl. Sci.* 65, 2018
- β+ emitters(PET):
  - INSIDE (CNAO) Bisogni *et al.*, J. Med. Imaging 4, 2017
  - J-PET (UJ) Baran *et al.*, MSS/MIC 2019
- Prompt-gamma radiation:
  - OncoRay+IBA (Dresden) Richter *et al.*, Radiotherapy and Oncology 1 118, 2016
  - MGH Boston Hueso-Gonzalez et al., PMB 63, 2018
  - Many others review: Wrońska, Dauvergne in *Radiation Detection Systems*, CRC Press 2021

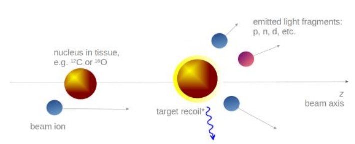
Prompt-gamma radiation (PG)

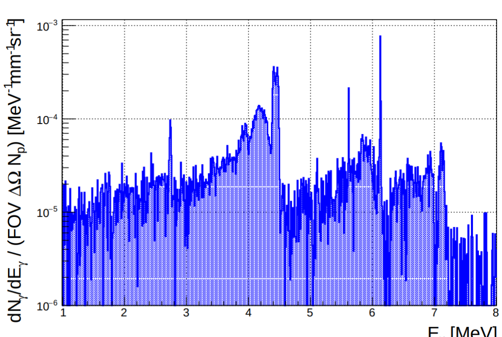
Status

- Beam range monitoring under tests in clinical conditions (PG spectroscopy, slit camera)
  Hueso-Gonzalez et al., PMB 63, 2018
  Richter et al., Radiotherapy and Oncology 1 118 , 2016
- 1d information

Dream

- Registeration of PG vertex distribution (Compton cameras)
- "Translation" of this distribution to the spatial distribution of deposited dose
  Liu, Huang Physica Medica 69, 2020
- Full 3d information





Wrońska, Dauvergne in *Radiation Detection Systems*, CRC Press 2021

PG – working conditions

- Large count rates ($n \times 10^5\ s^{-1}$)
- Typical spot: t=10 ms, N_p~10^8
- Background from other secondaries (neutrons)
- N_γ/N_p~0,15
- Energy range 1-7 MeV (continuum + discrete transitions)
- Detection system of large efficiency, rate capability and fast DAQ needed

PG – our activities

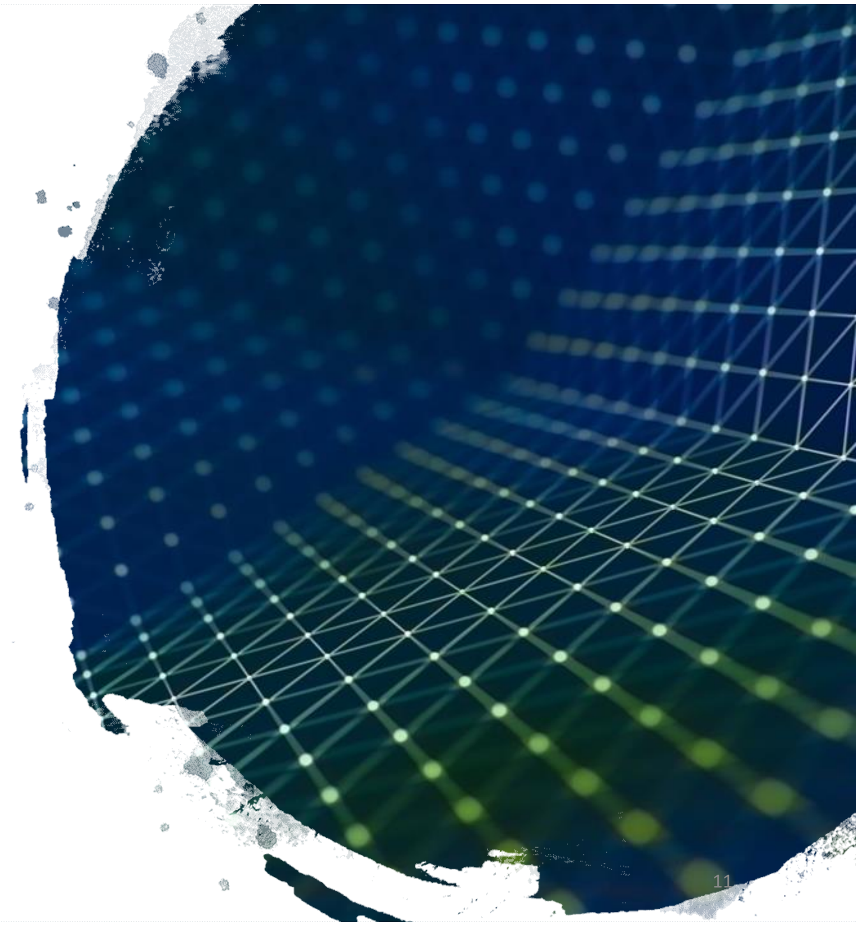
γCCB: characterization of PG – experiments

Monte-Carlo simulations + validation

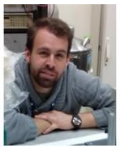
SiFi-CC Compton camera

Machine learning: event classification from CC

Beam-activated tumour tracers



The group

						
Aleksandra Wrońska[1]	Ronja Hetzel[2]	Rafał Lalik[1]	Andrzej Magiera[1]	Magdalena Rafecas[5]	Achim Stahl[2]	Mark Wong[1]
post-doc, PI	post-doc	post-doc	professor	professor	professor	post-doc
						
Jonas Kasper[2]	Magdalena Kołodziej[1]	Barbara Kołodziej[1]	Katarzyna Rusiecka[1]	Vitalii Urbanevych[1]		
PhD student	PhD student	PhD student	PhD student	PhD student		

Former members, also those working on the gCCB project:

Awal Awal[2], Piotr Bednarczyk[3], Anna Bekas[1], Daniel Böckenhoff[2], Arshiya Anees Ahmed[1], Arkadiusz Bubak[4], Richard Chomjak[1], Sabine Feyen[2], Grzegorz Gazdowicz[1], Aleksandra Kaszlikowska[1], Majid Kazemi Kozani[1], Laurent Kelleter[2], Nadia Kohlhase[5], Adam Konefał[4], Wojciech Kozyra[1], Karim Laihem[2], Johannes Leidner[2], Monika Łukowicz[1], Grzegorz Obrzud[1], Marek Pałka[1], Damian Stachura[1], Szymon Świstun[1], Aneta Wiśniewska[1], Anna Władyszewska[1], Mirosław Ziębliński[3]

[1]Institute of Physics, Jagiellonian University, Kraków [2]RWTH University, Aachen [3]Institute of Nuclear Physics PAN, Kraków [4]University of Silesia, Katowice [5]Institute of Medical Engineering, University of Lübeck

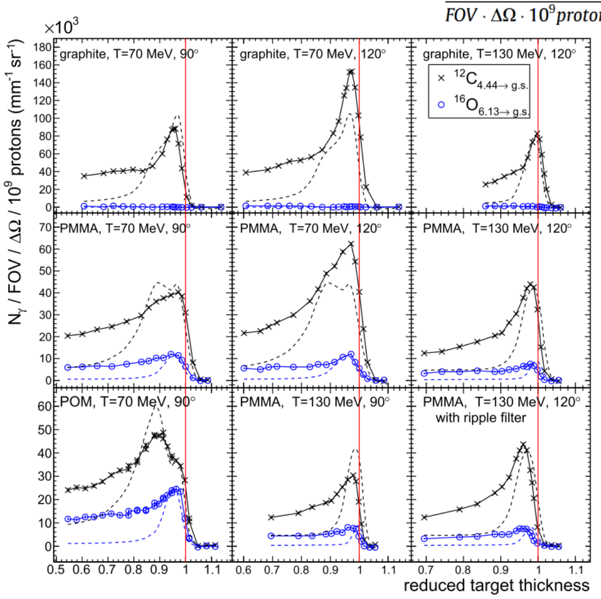
γCCB – experimental characterization of PG

$$\frac{N_\gamma}{FOV \cdot \Delta\Omega \cdot 10^9 protons}(\theta, z) = \frac{g(z) N_t}{FOV} \int \frac{d\sigma}{d\Omega}(\theta, E) f(E) dE$$

Beam attenuation from GEANT

Energy dependent angular distributions **from TALYS**

Proton energy distribution at given depth from GEANT



- Experiments: CCB, HIT, CCB
- Spectroscopy HPGe detector with ACS
- Phantoms with different elemental composition
- T_p=70, …, 230 MeV
- Different detection angles
- Focus: lines 4.44 MeV and 6.13 MeV
- Results confronted with TALYS and literature data
- Details of correlation PG-dose

Kelleter, Wrońska et al., Physica Medica 34, 2017
Wrońska et al., Acta Phys. Pol. B 48, 2017
Wrońska, Kasper et al., Physica Medica 88, 2021

γCCB – validation of simulations

- Comparison of simulated and measured PG emission from a PMMA phantom irradiated with proton beam
- Various G4 versions and physics lists
- Newest not always means best…
- Best match for G4 v10.4.2, QGSP_BIC_HP
- Theoretically better QGSP_BIC_AllHP does not reproduce line shapes
- …but best match also has issues (unphysical lines in spectrum)

GEANT4 A SIMULATION TOOLKIT

Beam energy (MeV)	Proton range (mm)	Beam current (nA)	Facility
70.54	35.06	0.5	HIT
130.87	105.46	0.5	HIT
130	104.23	50	CCB
180	184.10	10	CCB
230	280.35	1.5	CCB

Physics list	GEANT4 version	Label
QGSP_BIC_HP	10.4.2	A*
	10.5.1	B*
	10.6.3	C*
	10.7.1	D*
QGSP_BIC_AllHP	10.6.3	C•
	10.7.1	D•

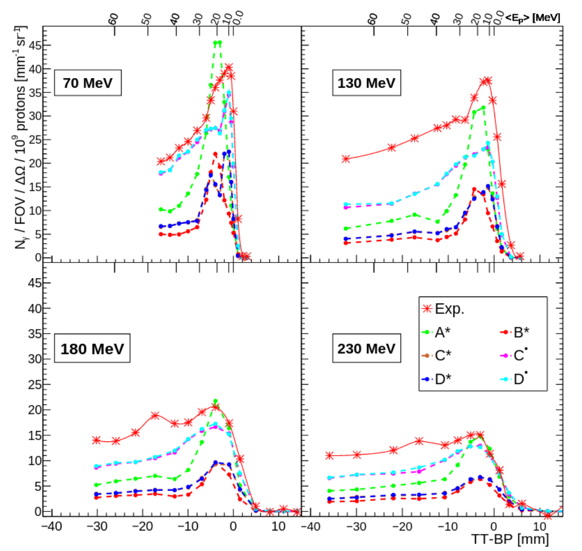
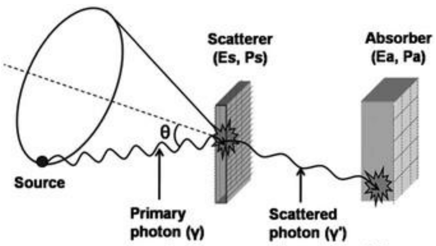


Figure 7: Comparison of gamma emission depth profiles for the 4.44 MeV line obtained from the simulations and the experiments for the beam energies 70 MeV, 130 MeV, 180 MeV and 230 MeV.

Wrońska, Kasper et al., Physica Medica 88, 2021

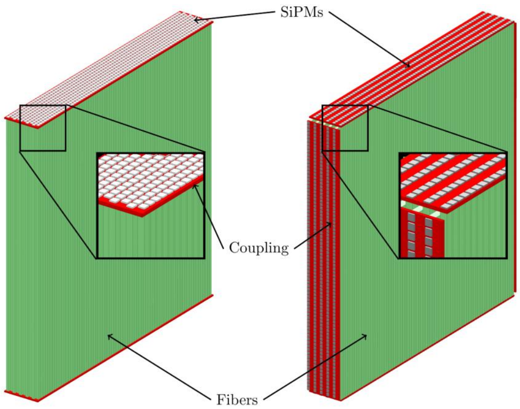


$$\theta = \cos^{-1}\left[1 + m_0c^2\left(\frac{1}{E_\gamma} - \frac{1}{E_{\gamma'}}\right)\right]$$

SiFi-CC: Compton camera for PGI

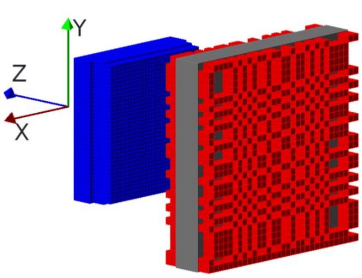
- **Si**PM and scintillating **Fi**bers based **C**ompton **C**amera
- Arrays of LYSO fibres => large efficiency
- 1mm x 1mm x 100 mm (small prototype)
  2mm x 2mm x 100 mm (full-scale)
- Dual readout via SiPMs:
  - 1:1 coupling (small)
  - 4:1 coupling (full-scale)
- Granularity => ~~pile-up~~ !
- DAQ with selective coincidence trigger => large data throughput

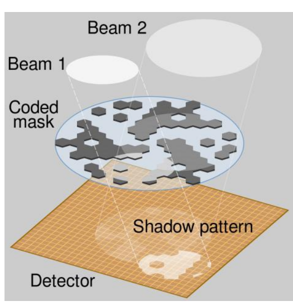
SiFi-CC



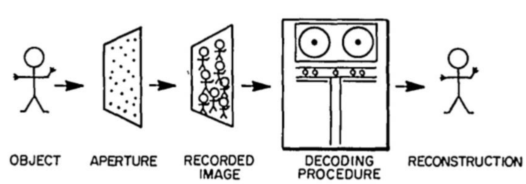
Kasper, Ph.D. thesis, RWTH Aachen, 2022

By-product: coded-mask setup (CM)





By Cmglee - Own work, CC BY-SA 3.0, https://commons.wikimedia.org/w/index.php?curid=47569900



E. E. Fenimore and T. M. Cannon, Coded aperture imaging with uniformly redundant arrays, Appl. Opt. 17, 337-347 (1978)

- Technique used in astronomy, also for γ sources (far field)
- So far not tested experimentally for PT Sun *et al.*, Rad. Phys. Chem. 174 (2020)
- 2d image
- Larger statistics than in a single-aperture camera
- **Will this work for the near field?**

SiFi-CC - prototyping

- ✓ Investigation of fibre properties
  - Energy resolution?
  - Position resolution (along the fibre)?

Rusiecka *et al.*, ISMART2018 (Springer)
Rusiecka et al., JINST 16, 2021

- ✓ Construction of a small module prototype
  - 4 layers
  - 64 fibres
  - re-arrangable

Rusiecka, PhD thesis in preparation, Jag. Uni. 2022

- ✓ Data analysis software

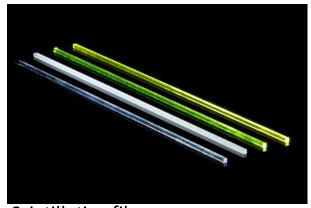
J. Kasper, PhD thesis, RWTH Aachen 2022

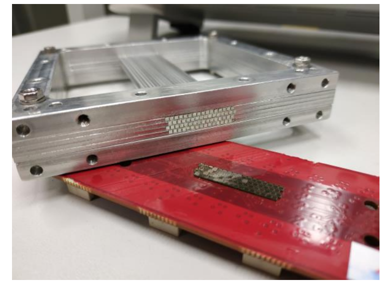
- Image reconstruction software

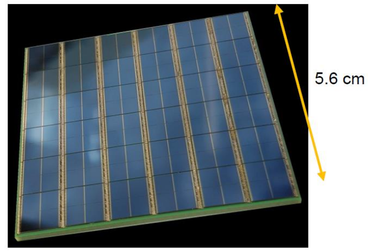
Kohlhase *et al.*, IEEE Trans. Rad. Plas. Med. Sci. 4, 2020

- FEE+DAQ – classical/digital SiPMs

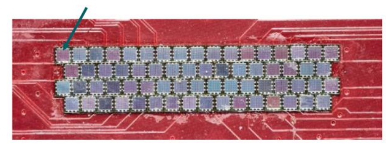
Schug, Schulz *et al.*, PMB 61, 2016

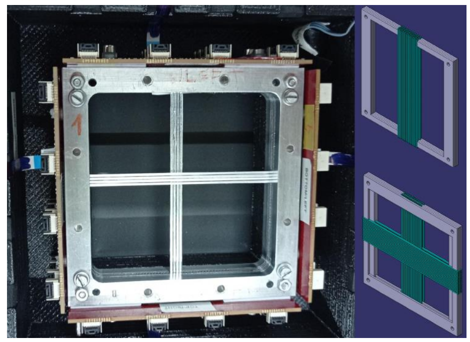

Scintillating fibres





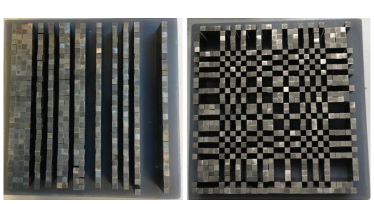
PMI Power Tile Phillips, digital SiPMs

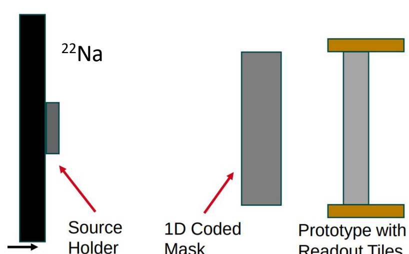
1 mm x 1mm

Classical SiPMs custom array

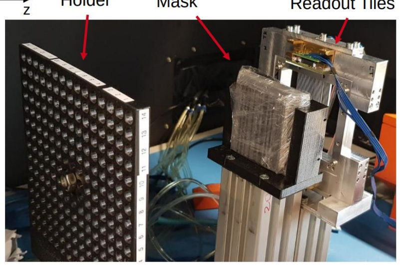


SiFi-CC – setup lab tests

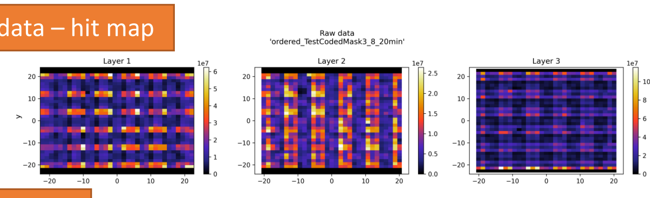
- Calibration
- Collective effects (optical cross-talk)
- Test CC setup:
  - Our prototype module as scatterer
  - A PET module as absorber
  - PowerTiles
  - Analysis in progress
- Test CM setup
  - 1d with our prototype + PowerTiles
  - 2d with PET stack + PowerTiles
  - Promising results
  - Next step: continuous source

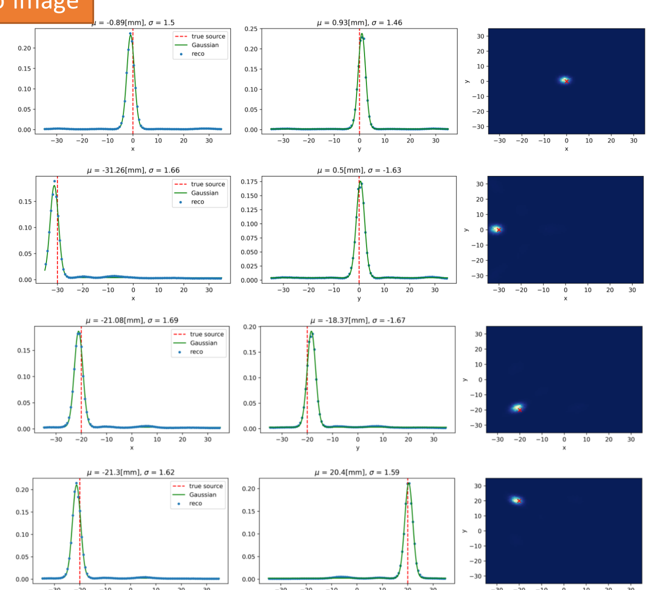






S. Müller, DPG SM 2022

Raw data – hit map


Reco image


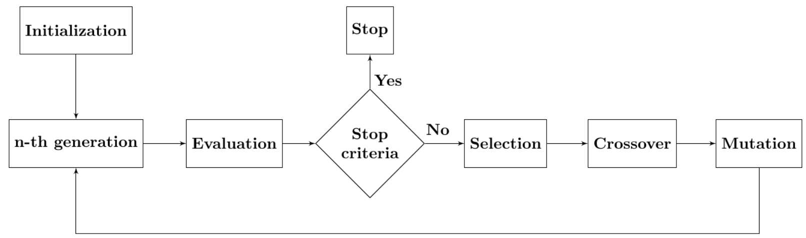
V. Urbanevych

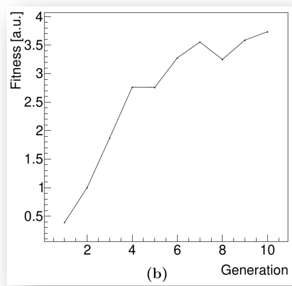
SiFi-CC – optimization – genetic algorithm

- Geometry optimization and rate estimation
- Simulation framework including... everything! (light propagation, PDE, event mixing, random coincidences, pile-ups, dead time, etc.)
- Simulation parameters tuned against lab measurements
- Genetic algorithm as a tool for multi-parameter optimization

  Yang, *Nature-Inspired Optimization Algorithms*, Academic Press 2021

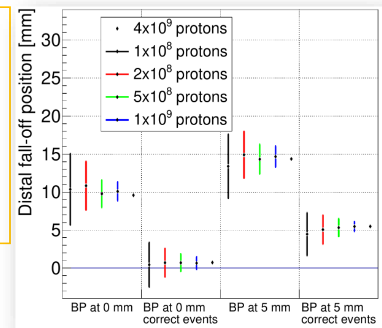
- Optimization targets
  - Source-scatterer distance
  - Scatterer-absorber distance
  - Scatterer thickness
  - Absorber thickness
- Metric = fitness function incl.:
  - Signal statistics
  - Background
  - Efficiency of background suppression
  - Obtained image resolution





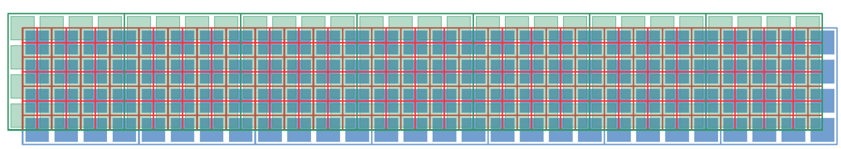
Results for individually read out 1x1x100 mm^3 fibres:

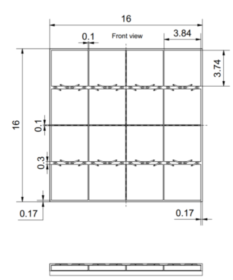
- Source-scatterer distance 150 mm
- Scatterer-absorber distance 120 mm
- Scatterer thickness 16 layers
- Absorber thickness 36 layers

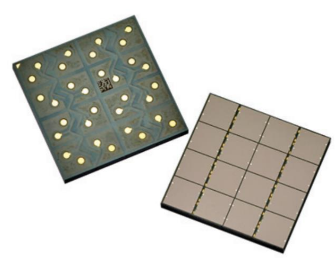


Kasper, Ph.D. thesis, RWTH Aachen, 2022

Roadmap to the full-scale SiFi-CC







- 4:1 fiber-SiPM coupling (budget reasons)
  - Diagonal shift of the upper and lower SiPM arrays by ½ pixel pitch to enhance fibre identification
- We chose SiPM arrays [AFBR-S4N44P164M:]()
  - 4x4 pixels, 16x16 mm^2
  - Microcell pitch 40 um
  - 8334 microcells per SiPM
  - PDE 68% (!)
- PETSYS DAQ system
  - TOFPET ASICs recently equipped with ADC
  - Small dead time
  - Scalability
  - Good price/performance
- Geometry:
  - Scatterer: 7 layers, 55 fibres/layer
  - Absorber: 15 layers, 63 fibres/layer
  - Fibre pitch: 2 mm

Today: SiPMs already in lab; DAQ system in lab; Sci fibres ordered; Support in production

End of Nov: Scintillating fibres arrive

December: Put components together, test with sources

2023

January: Test with beam@CCB — CM mode

Rest of 2023: Build absorber and continue with CC-mode...

~May: Test with beam@CCB — CC mode

Machine learning for CC event classification

Event selection for image reconstruction:

- Scatterer-absorber coincidences
- >1 cluster/module? Select properly!

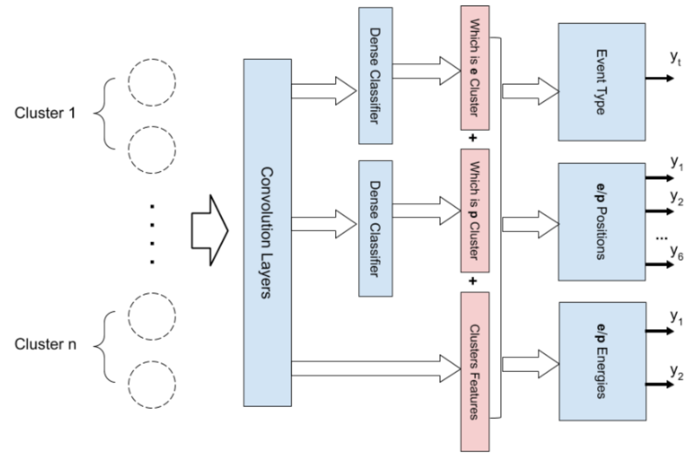
$$\{\vec{r}_i,\ \vec{\sigma}_{r_i},\ \Delta E_i,\ \sigma_{\Delta E_i}\}_{i=1\cdots N} \longrightarrow \{\vec{r}_e,\ E_e,\ \vec{r}_{\gamma'},\ E_{\gamma'}\}$$

Approaches:

- Set of classical 1d cuts
- Neural network (Python)
  Awal, M.Sc. thesis, RWTH Aachen, 2020
- Various MLT (ROOT TMVA)
  Kazemi Kozani, PhD thesis, Jag. Uni. 2022
  Kazemi Kozani, PMB 67, 2022

	Efficiency	Purity
Classical cuts	14.3%	5.6%
Neural network (Python)	20.6%	10.4%
TMVA (ROOT)*	11.4%	25.9%

* data set w/o random coincidence bg



Compton?

Assign energies and positions e' i γ'

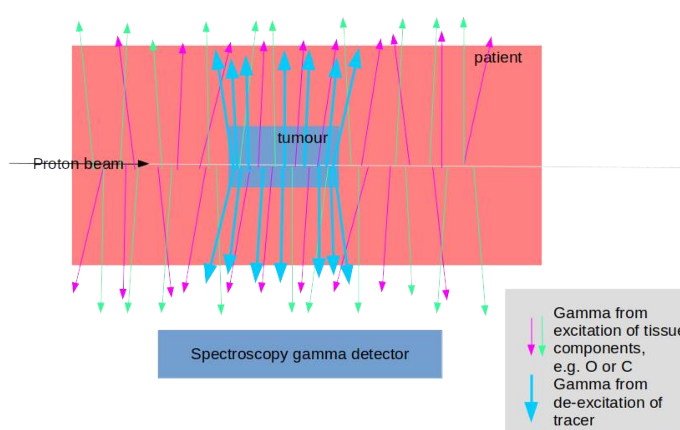
Awal, M.Sc. thesis, RWTH Aachen, 2020

SiFi-CC

Beam-activated tumour tracers

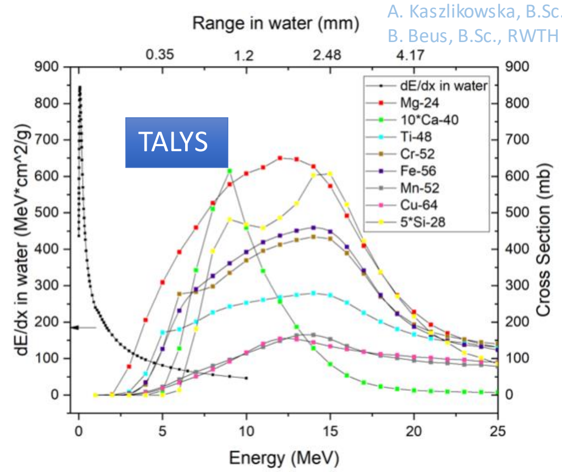
- PG = a footprint of elemental composition
- Are cancerous tissues significantly different from the healthy ones? NOT ALL
  Cai et al., Molecules 25, 2020
  Maughan et al., Med. Phys. 24, 1997
- Can we selectively deliver a selected element to tumour?? YES (PET, BNCT)
- Limitations:
  - Lack of toxicity
  - Absent in body
  - Selective delivery feasible
  - Stable, emits gamma only when excited by proton beam
  - Unique energy of discrete transitions, preferably 1.5-3 MeV
  - Short deexcitation time
  - Large cross section at Bragg peak, i.e. for small proton energies
- Similar in concept (though inversed logic) to
  Magalhaes Martins, Sci. Rep. 11, 2021
- Method proposed by several people about the same time (A. Stahl, G. Gazdowicz from SiFi-CC, also G. Cartechini from Trento Uni.)
  https://agenda.infn.it/event/23656/contributions/120652/

Idea in a cartoon



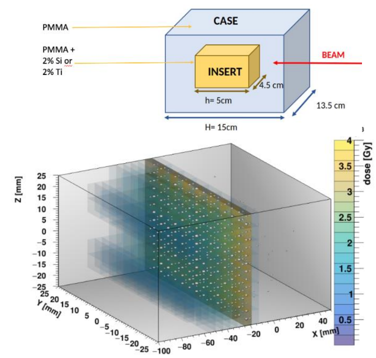
Search for tracers

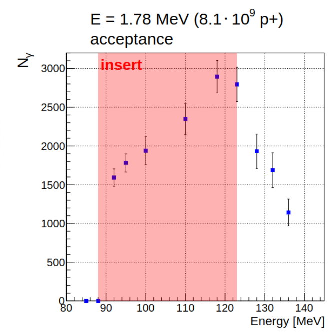
A. Kaszlikowska, B.Sc., Jag Uni, 2021
B. Beus, B.Sc., RWTH Aachen, 2021



- Promising σ(E) dependence: Mg, Ca, Si
- Simulations needed to assess signal significance
- How to selectively deliver to tumour? Nanoparticles! Collaboration with group of M. Parlińska from INP PAS in Kraków
- Initial results:
  - 2% mass concentration feasible for Si and Ti (MTS tests)
  - Signal appears for a proximal layer when BP contained in the tumour
  - Signal drops when BP moves downstream of tumour
  - Pilot beam time with a HPGe detector – no observation, too poor S/B, ACS necessary

B. Kołodziej, M.Sc., Jag Uni, 2022





Summary

PG radiation is a hot topic in medical physics

Within the γCCB and SiFi-CC projects:

- We characterized in detail the PG emission in PT
- We validated the simulation tools (GEANT4, TALYS)
- We are building a Compton camera for beam range monitoring in PT
- We are developing methods for CC event classification
- We are testing a method of tumour markers activated by a proton beam