CERN

European Organization for Nuclear Research
Organisation Européenne pour la Recherche Nucléaire

Medical Applications at CERN

Austrian Teachers Program, November 18, 2011

Hartmut Hillemanns
Hartmut.hillemanns@cern.ch

Index

CERN & fundamental research characteristics

Research results for health that strongly impacted society

How research can help society meet challenges ahead

- Health
- Molecular biology

CERN...

Seeking answers to questions about the Universe

Advancing the frontiers of technology

Training the scientists of tomorrow

Bringing nations together through science

Particle, Astro-Particle & Nuclear Physics research characteristics

Large projects requiring long and Intensive R&D and Prototyping

- Source of innovation
- Source of new technologies and expertise
- Existing technologies pushed to the limits

Highly collaborative international open science environment offering top quality education from apprentice to post-doctoral

- Shared research results

World standard institutions (centres of excellence) with high tech laboratories for:

- Accelerator elements, Vacuum technologies, magnets
- Particle detectors
- Electronics & IT
- Super-conductivity and Cryogenics
- Mechanics & surface Treatments

CERN

the world largest particle physics laboratory where scientific knowledge and technology are transferred to industry and society

Fundamental research and its impact on society

Research results have contributed to the development of major applications that strongly impacted society

- Health: Devices to assist clinicians in diagnostic and therapy
- Information and Communication Technology: WWW, A fundamental change in dealing with digital information

Technology developments motivated by the current research programme can help society meet challenges

- Health
  - Defeating cancer
- Molecular biology
  - Providing biologist an insight on the fundamental mechanisms of Life
- Information society
  - The seed of IT's next generation
- Sustainable energy and environment
  - Improved energy collection production and management

Index

CERN & fundamental research characteristics

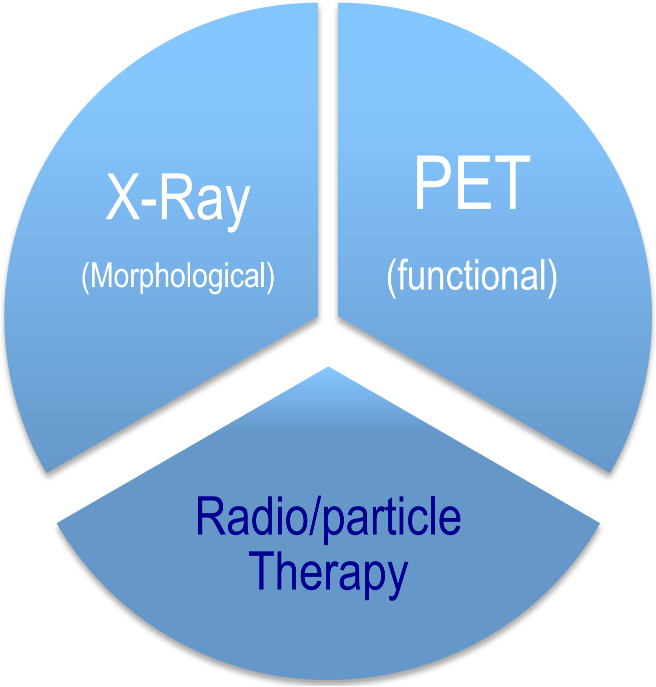
Research results for health that strongly impacted society

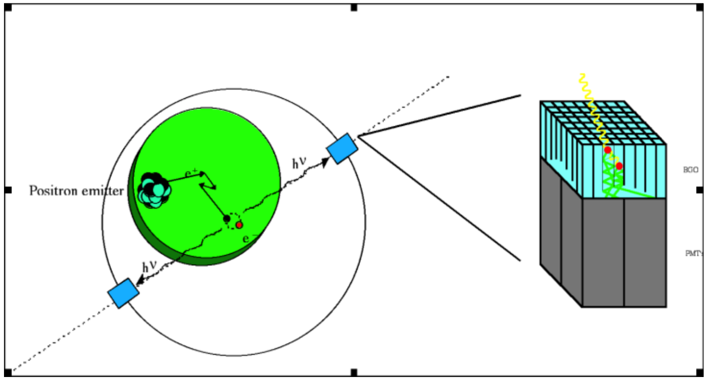
How research can help society meet challenges ahead

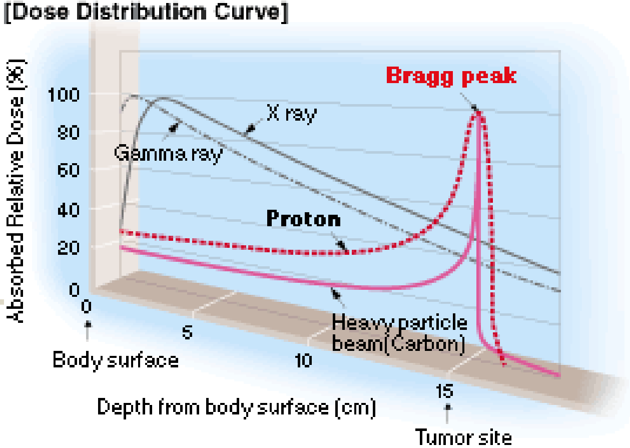
- Health
- Molecular biology

Physics and Medicine : a century of collaboration

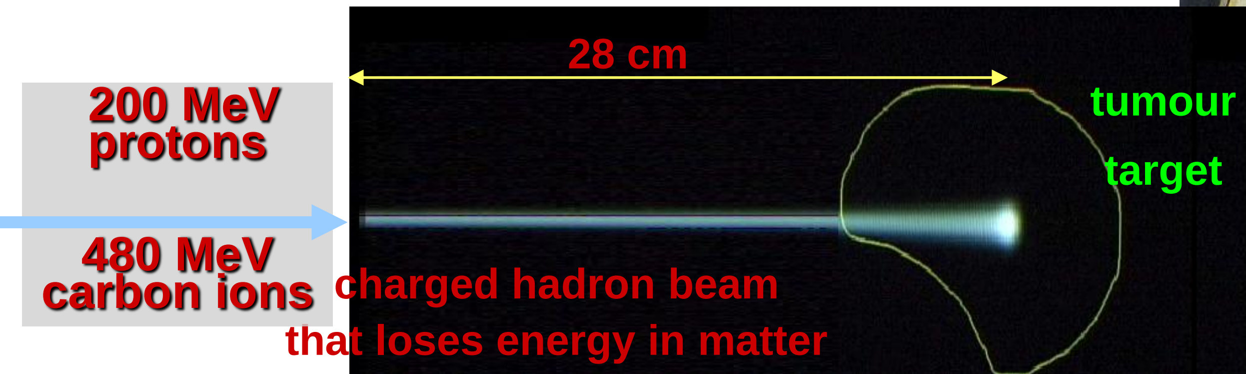
Technology and instrumentation for diagnosis and treatment:





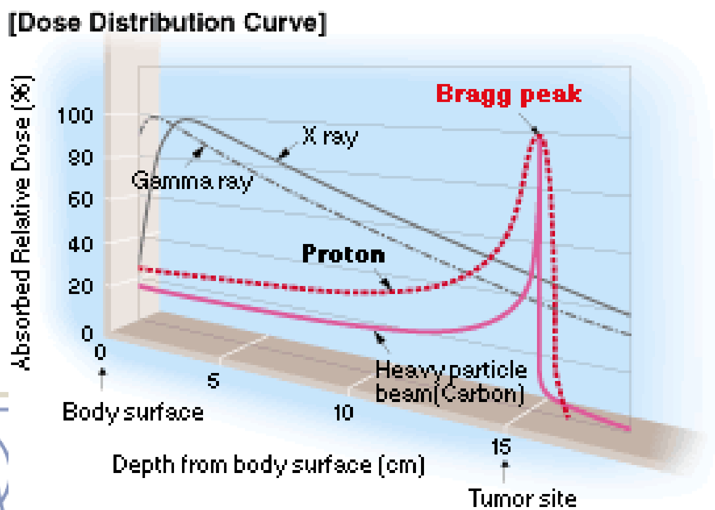


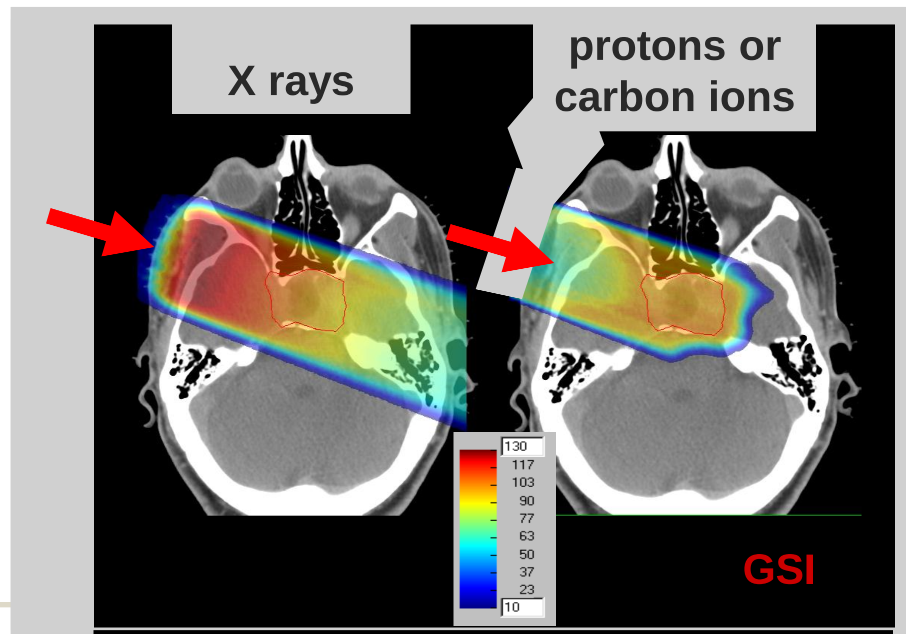
Hadron Therapy



Hadron beams provide new treatment opportunities for deep-seated tumours.

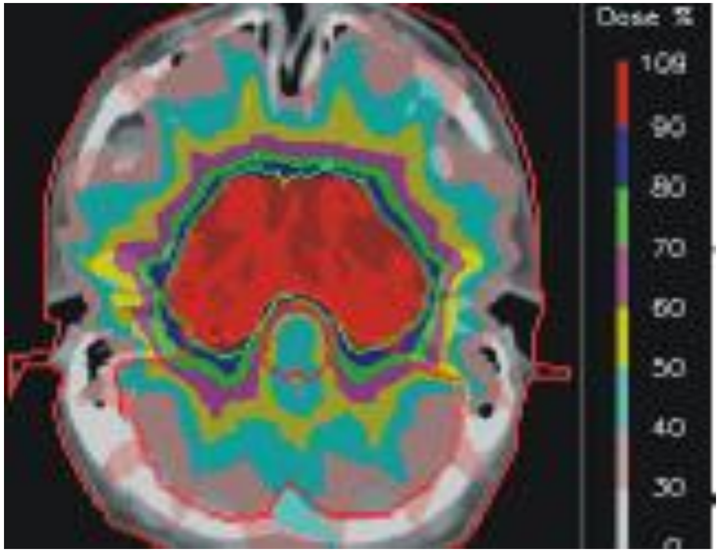
Hadron beams are more effective than X-rays in destroying tumours while sparing healthy tissues nearby.



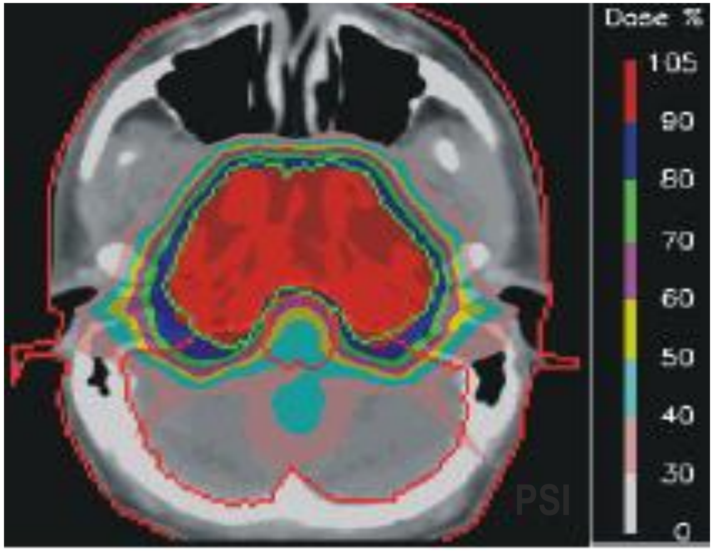


Protons are quantitatively different from X-rays

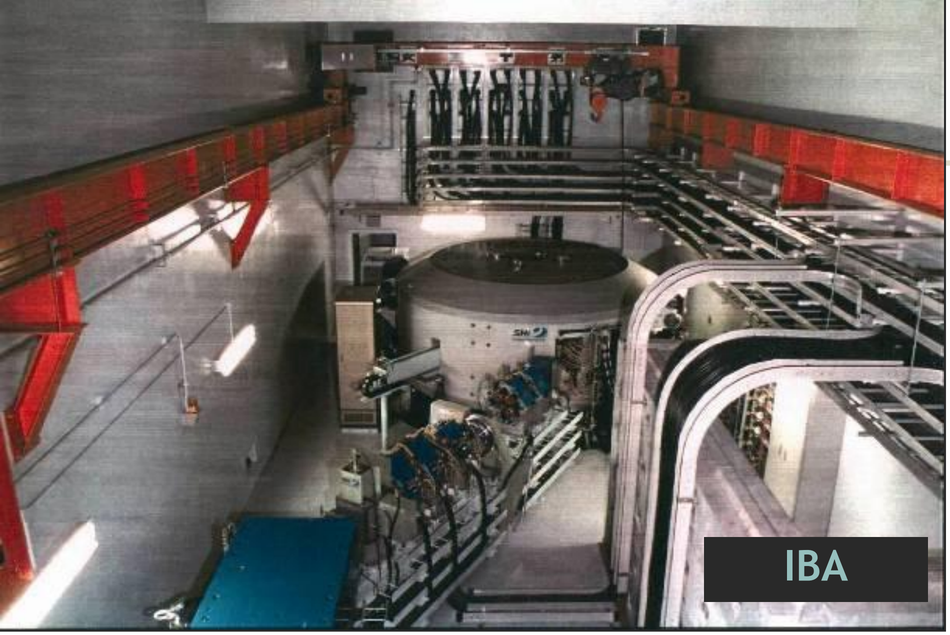
9 X-ray fields

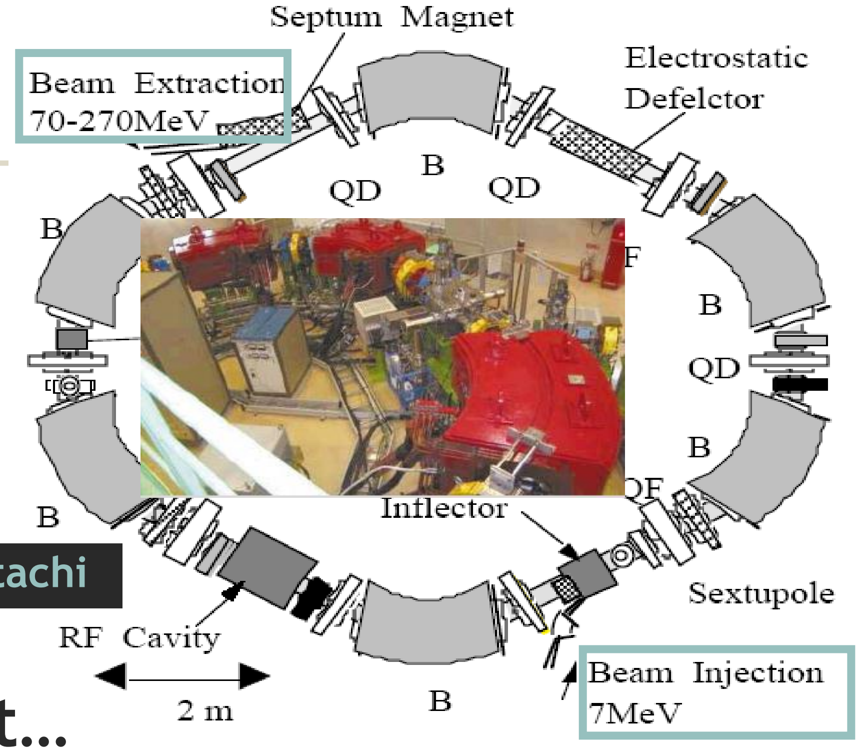


4 proton fields



- Carbon ions deposit in a cell 24 times more energy than a proton producing not reparable multiple close-by double strand breaks
- Carbon ions can control radio-resistant tumours





Protontherapy: a mature market…

Cyclotron solution for protons by IBA - Belgium

Five companies offer turn-key centres for 100 M€.

If proton accelerators were ‘small’ and ‘cheap’, no radiotherapist would use X rays.

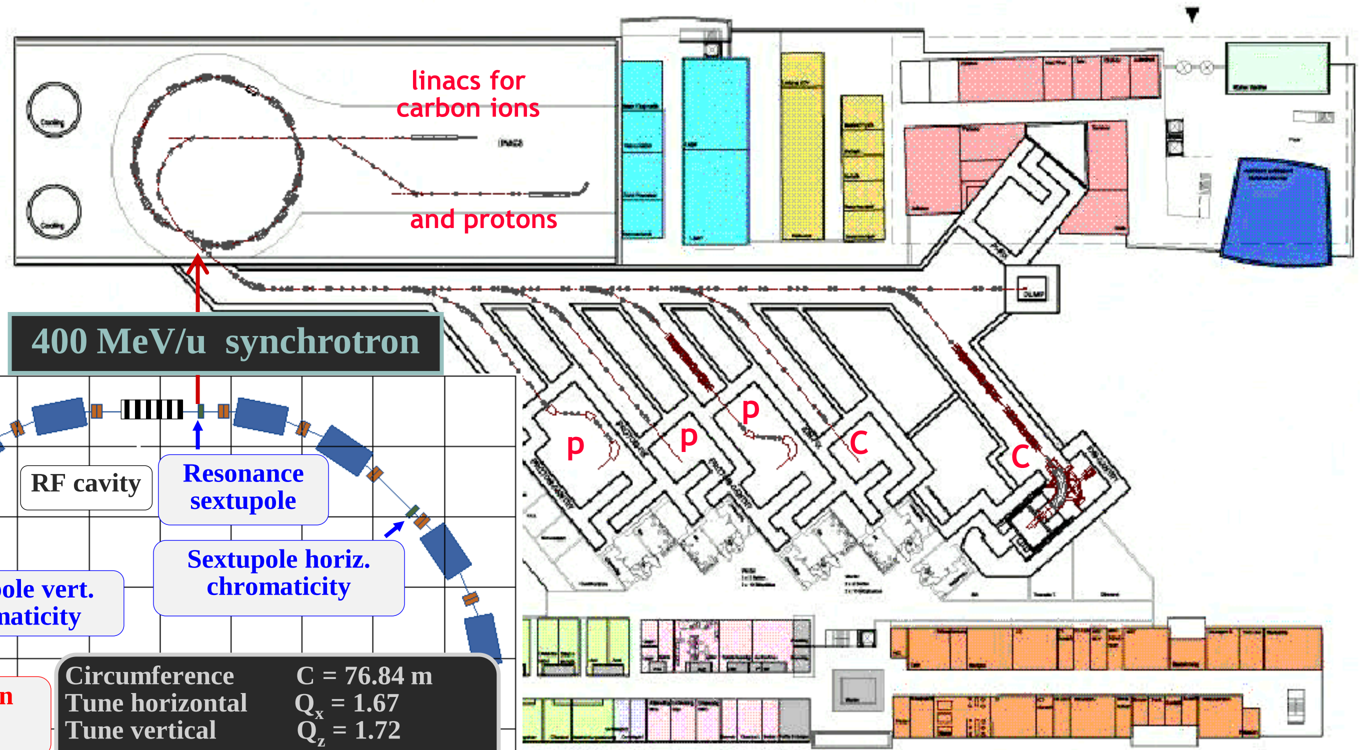
Radiotherapy is the main user of Linear accelerators

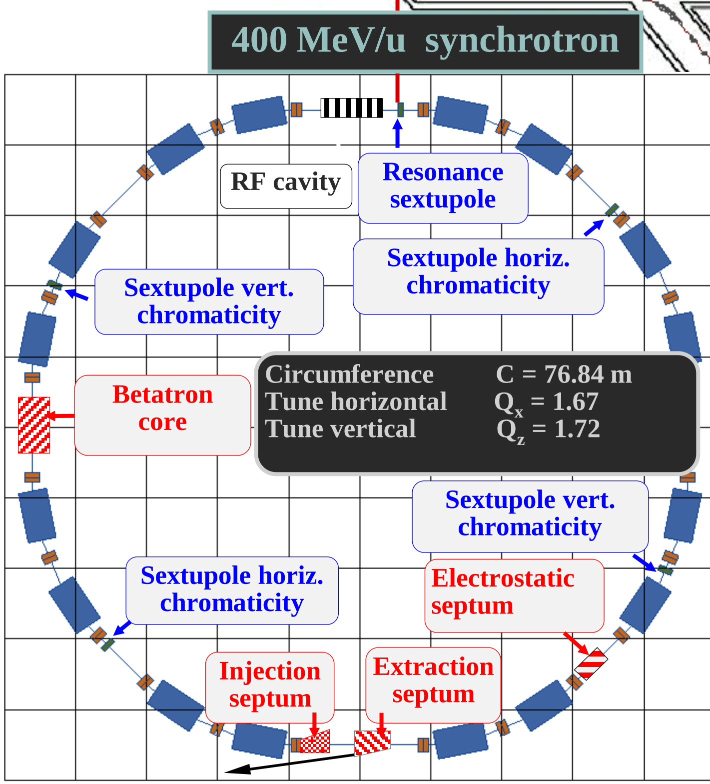
CATEGORY OF ACCELERATORS	Number in use (2005)
High Energy acc. (E >1GeV)	~ 120
Synchrotron radiation sources	> 100
Medical radioisotope production	~ 200
Radiotherapy accelerators *	> 7500
Research acc. including biomedical research	~ 1500
Acc. for industrial processing and research	~ 1500
Ion implanters, surface modification	> 7000
Total	> 17500

*** Linacs used in radiotherapy represent 40% of all running accelerators:**
France, Germany, Italy: 4 units per million inhabitants
Switzerland: 11 units per million inhabitants
Finland: 14 units per million inhabitants

Hadron therapy: PIMM Study at CERN in 1996 - 2000

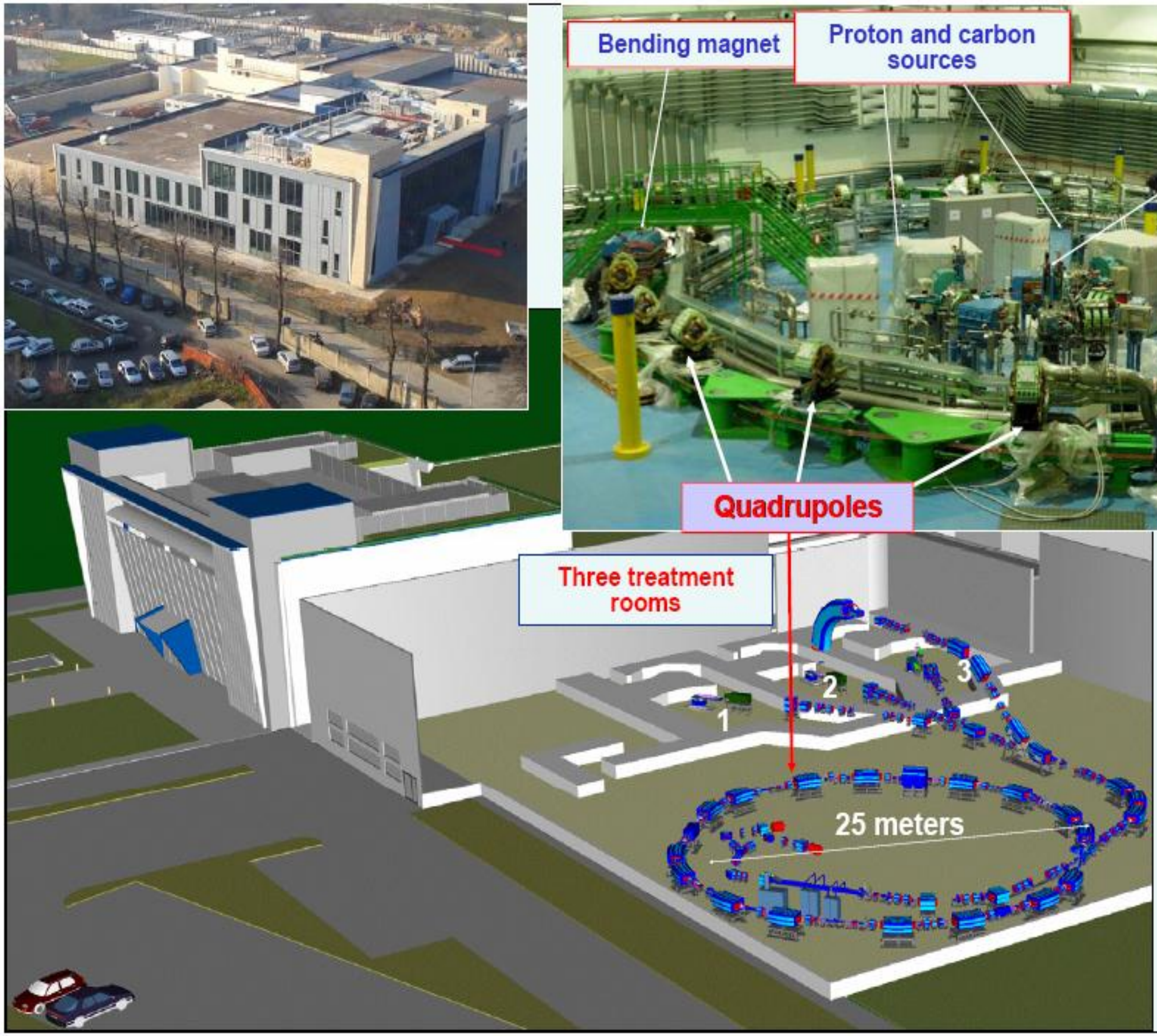
CERN–TERA–MedAustron Collaboration for optimized medical synchrotron (protons and carbon ions) Project leader: P. Bryant





16 Bending Magnets
3 extraction systems:
- **<u>betatron core</u>**
- **1/3 resonance**
- **RF knock-out**

CNAO: The Hadron facility in Pavia

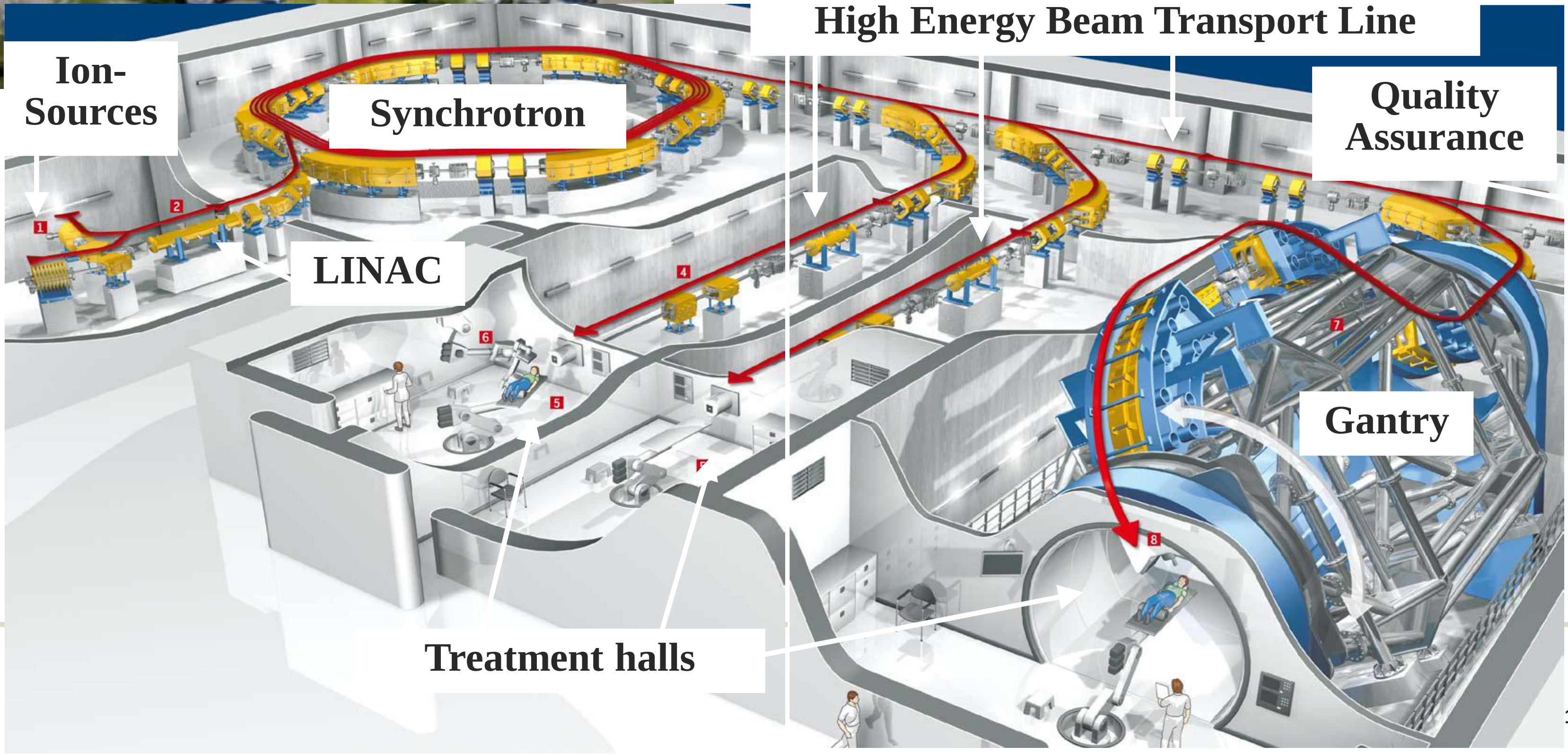


CNAO
Centro Nazionale di
Adroterapia Oncologica
Pavia

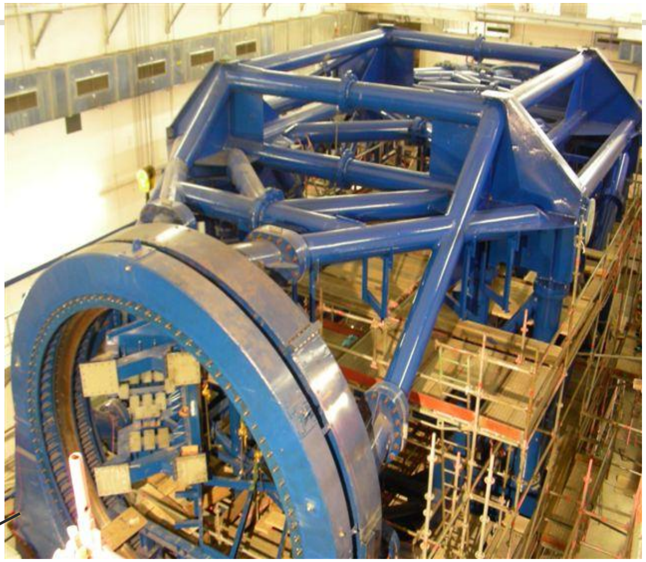
Beams ready: end 2008

The site of HIT
the Heidelberg Ion Therapy

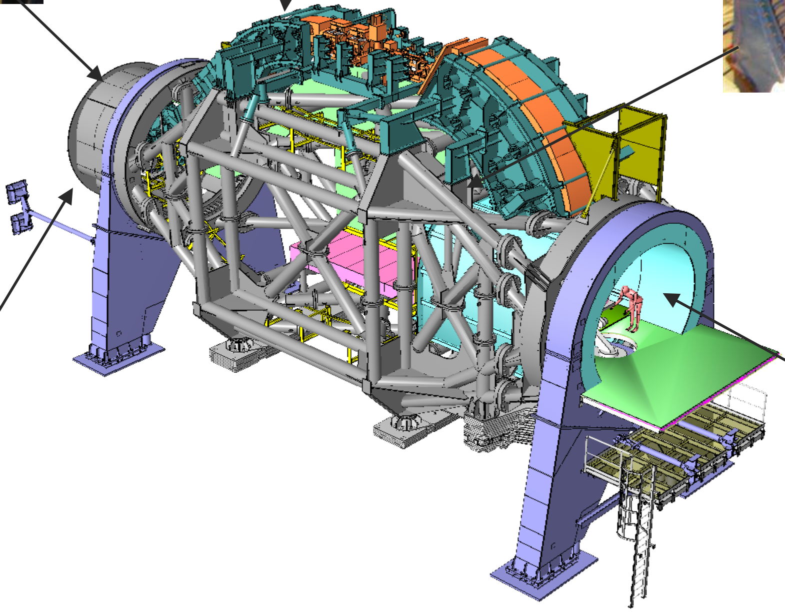
A € 100M project with gantry for beam rotation
Collaboration with GSI and SIEMENS for the
Construction of the facility
First beam extracted in 2007
First patient: October 2008



Heidelberg ion gantry: 600 tons and 400 kW



1. Rotation at 21.04.2007



Science to Health: Hadron Therapy

Technology

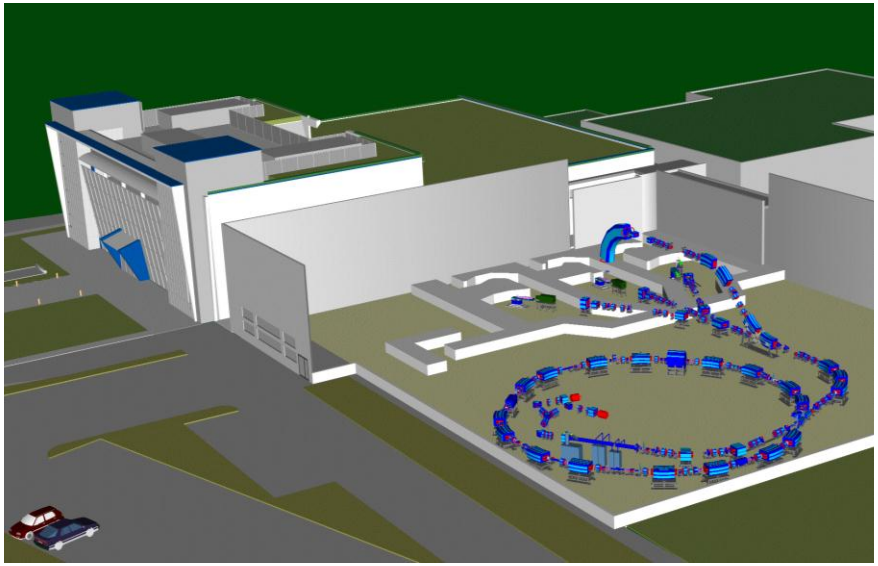
Complex accelerator technology in combination with precise imaging systems developed for PP constitute the infrastructure for hadron therapy centers.
(ex. PIMMS Design Study (published in 2000))

Health care

- Protons and ions have proved to be extremely efficient to treat deep seated tumors without damaging healthy tissue.
- Effective also for radio resistive tumors

Impact

- CERN has contributed to the construction of CNAO (Padova, Italy) which is close to commissioning.
- In 2008: CERN has started a collaboration with MedAustron for the construction of a hadron therapy center in Austria.
- Construction costs for the infrastructure of such center is approximately 120 Million EUR. Annual running costs 15 Million EUR.



Science to Health: Radiopharmaceuticals

Technology

- Isotopes produced in reactors and accelerators
- Advanced accelerator technologies developed in PP enable large scale production and secure supply

Health care

Medical isotopes instrumental for:

- accurate diagnostics through medical imaging
- cancer therapy

Business impact

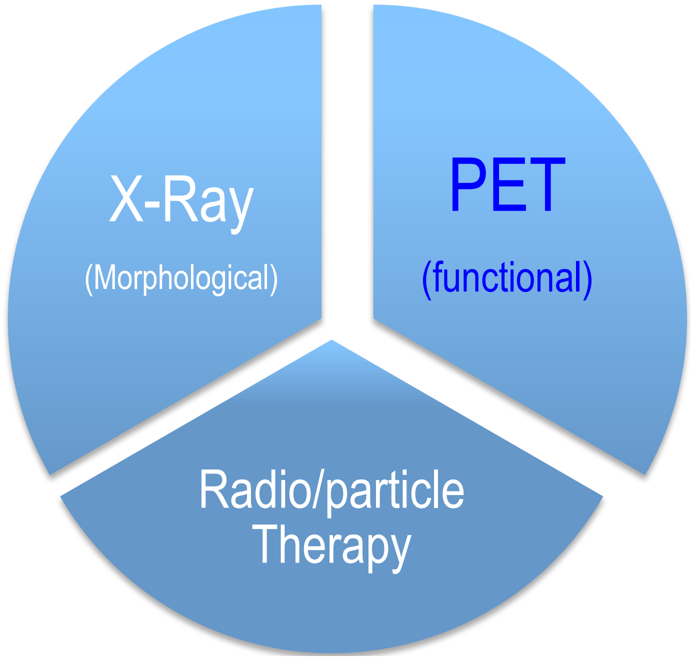
Strong increase in demand expected. Market for diagnostic and therapeutic isotopes forecasted a 10% annual growth and should reach 4.5 Bn Euros in 2020.

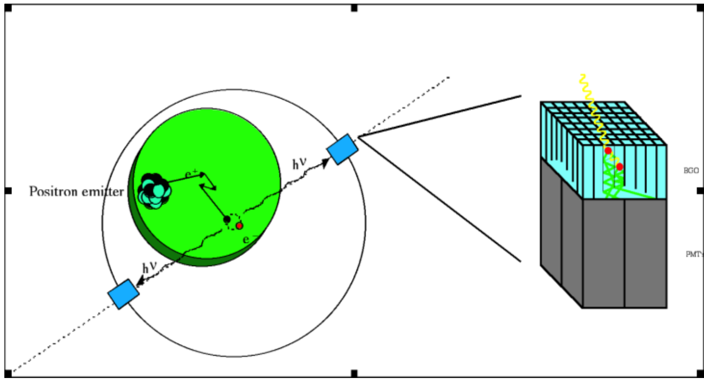
Year:	*2005*	*2010*	*2015*	*2020*
Diagnostic (M EUR)	*987*	*1589*	*2559*	*4121*
Therapeutic (M EUR)	*89*	*143*	*230*	*372*

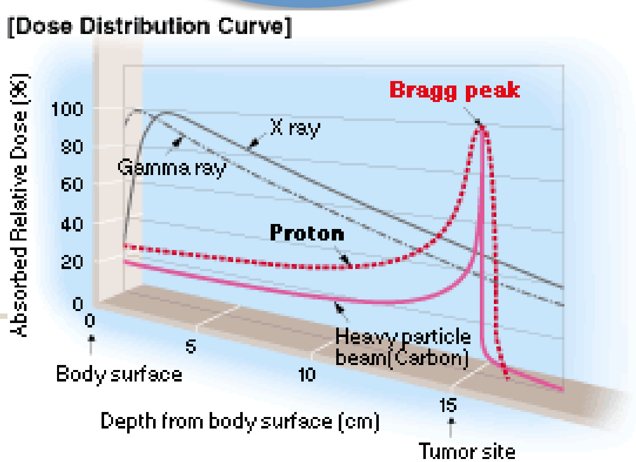
Source: Frost & Sullivan

Physics and Medicine : a century of collaboration

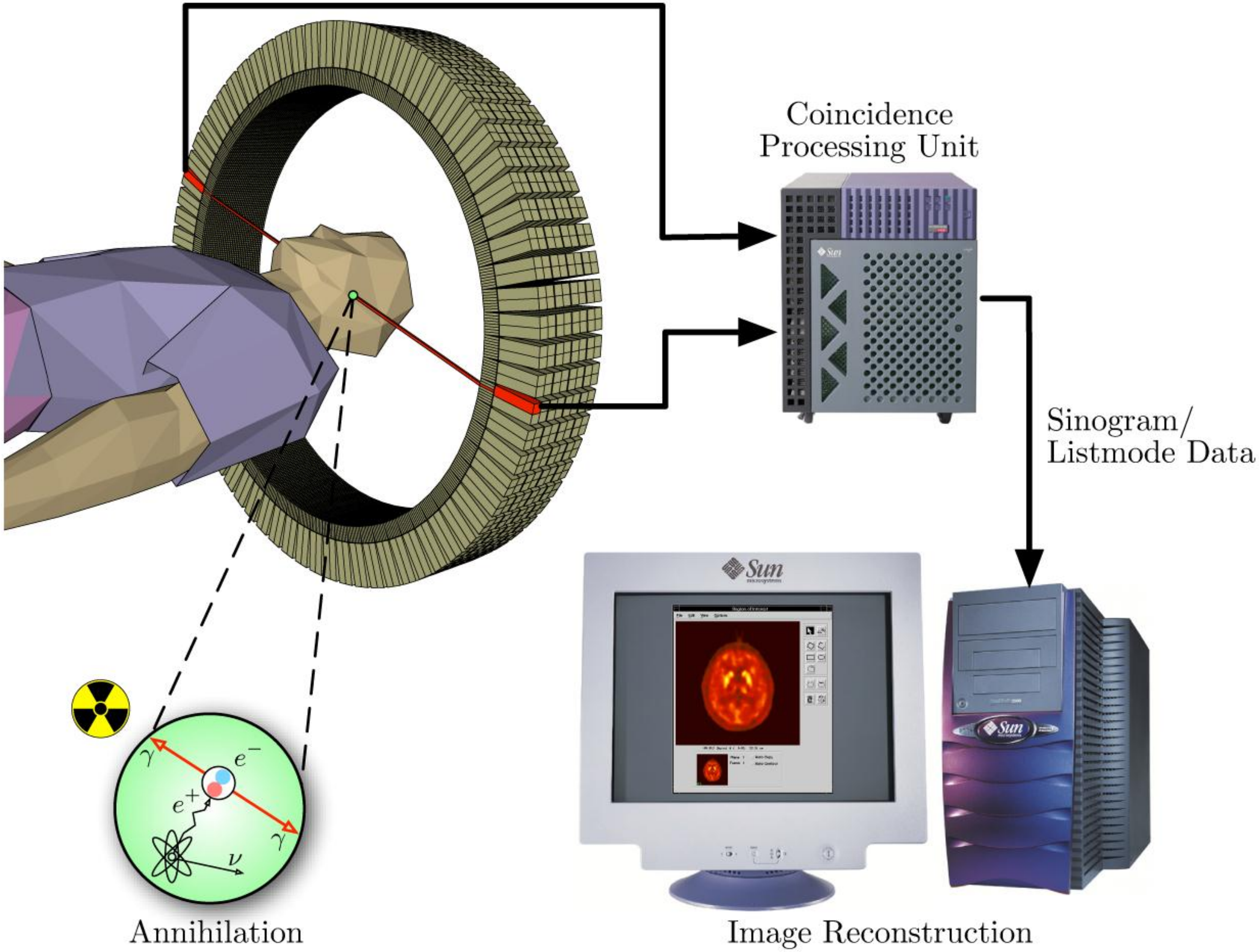
Technology and instrumentation for diagnosis and treatment:





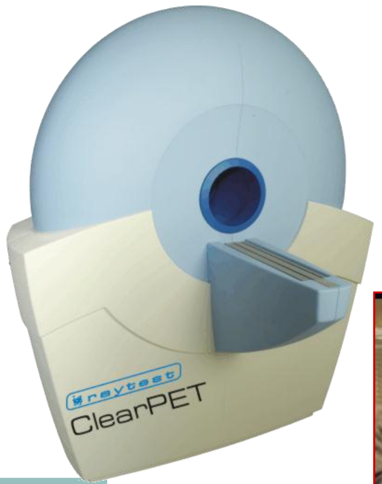


PET (Position Emission Tomography)



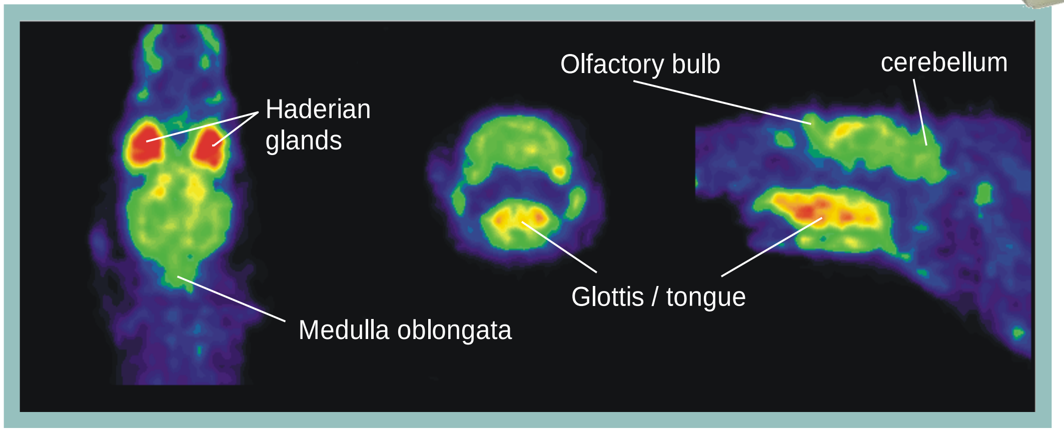
PET: a key device for functional imaging

- **Generalized use of PET technologies across multiple domains of medical diagnostics**
  - **Neuro-sciences**
  - **Cancer treatment planning**
  - **Small animal PET for drug discovery**
- **Dedicated PET:**
  - **Mammography,**
  - **Brain devices**



Whole-body PET/CT market

Year	*Mio $*
2004	***880***
2005	***985***
2010 (est.)	***1870***



Crystal Clear Collaboration: Small animal PET for in-vivo drug screening

PET technologies

Radiopharmaceuticals

- Tracers: functional specificity
  - Most popular: FDG (Fluorodesoxyglucose)
- Markers: attached to tracer to generate γγ (511 keV) signal
  - Ex: ^{18}F, ^{11}C
- α-therapy

Detectors

- Photo-converting material (Matrices of mono crystals), ex: LSO, LYSO, GSO

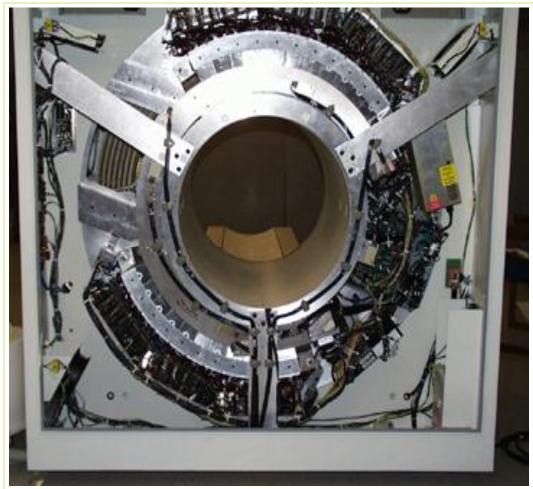
Electronics

- Photo-multipliers
- Avalanche Photo Diodes (APD)
- In the future Single Photon Avalanche Photo Diodes (SPADS) (Higher Gain)

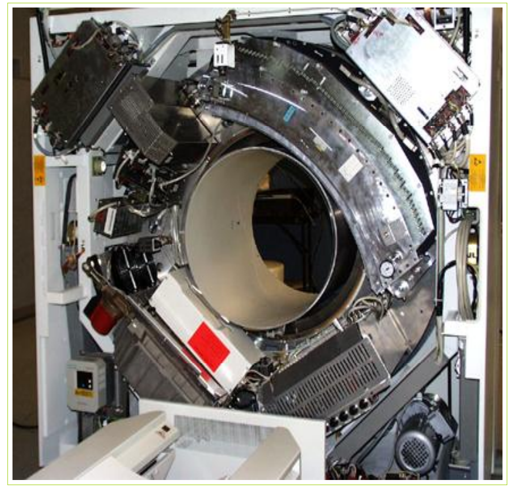
Software

- Sinograms for image reconstruction

Software to combine modalities: Image fusion: PET + CT

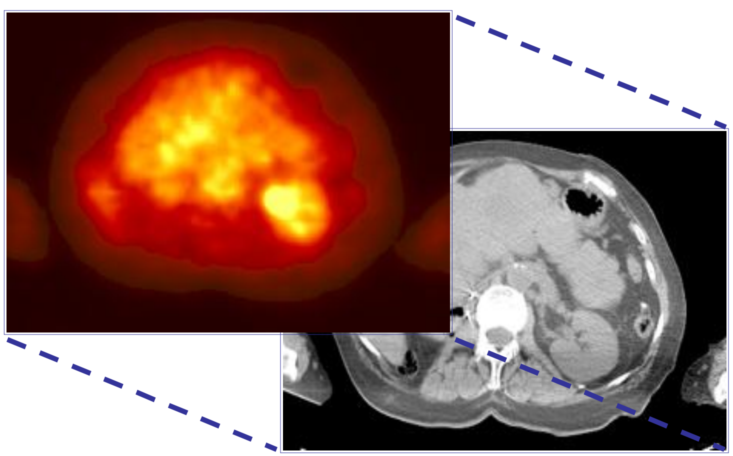


ECAT ART



Somatom AR.SP

SMART scanner



PET + CT

from University of Pittsburgh & Siemens

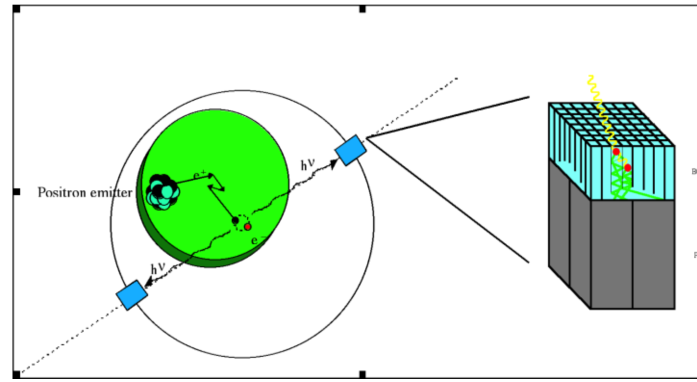
Physics and Medicine : a century of collaboration

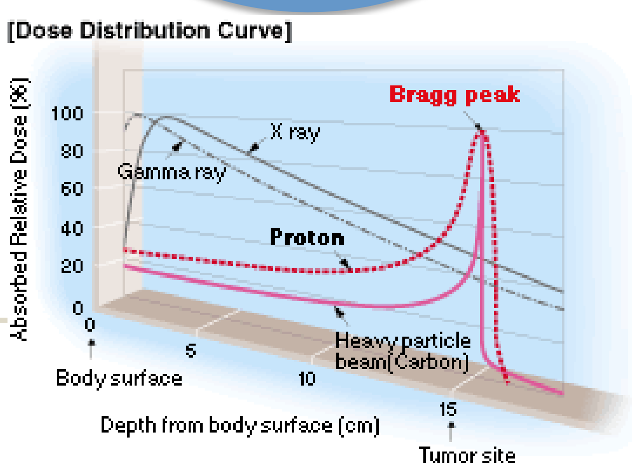
Technology and instrumentation for diagnosis and treatment:

X-Ray
(Morphological)

PET
(functional)

Radio/particle
Therapy

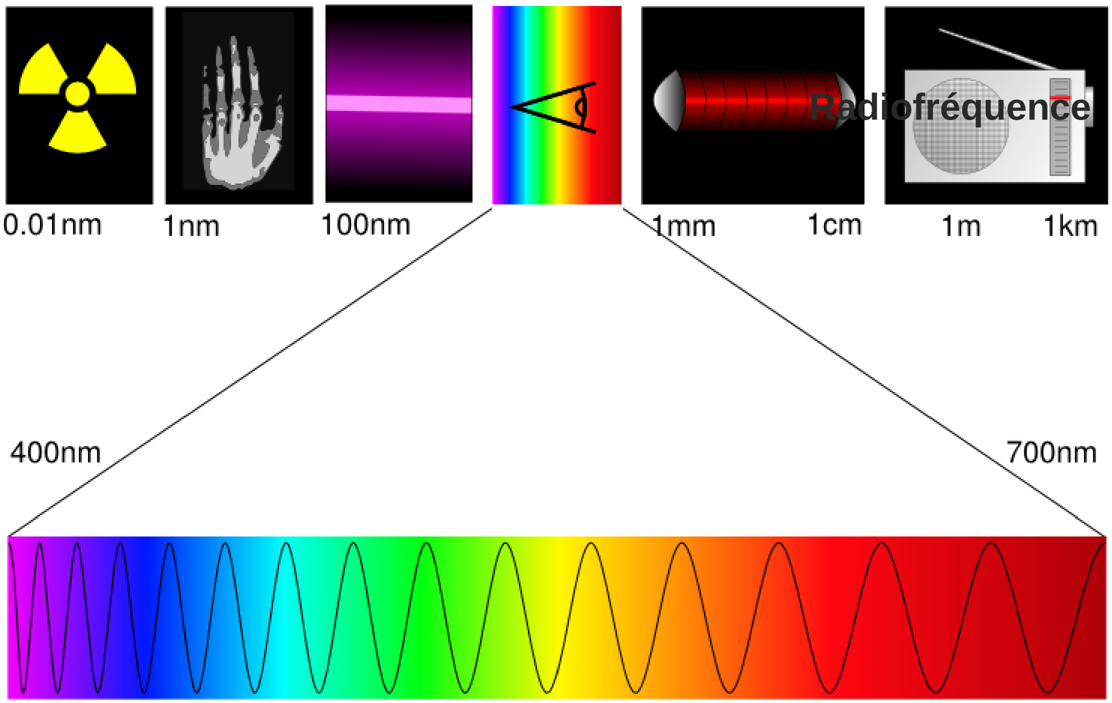


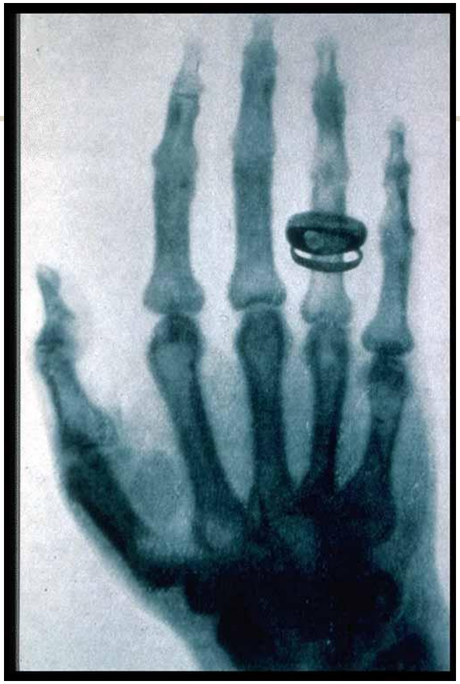


X Rays to CT

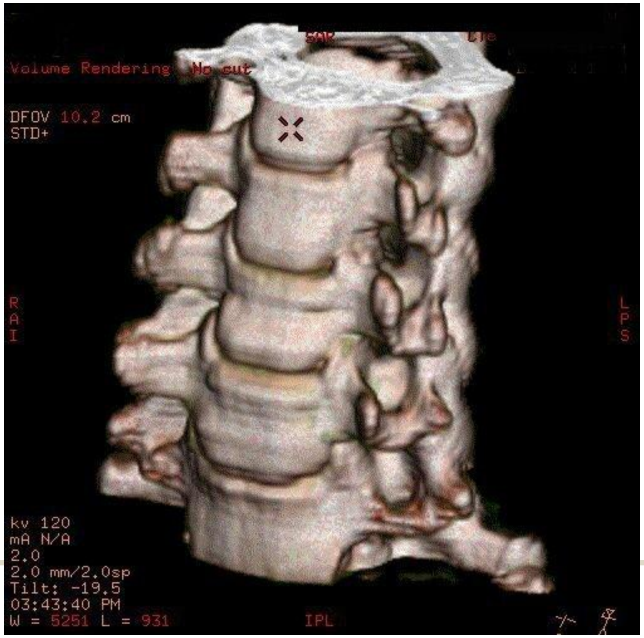
Since 1895, 30 – 100 kEV

Originally: Sensitive film
Today: Digital radiography, Computed tomography (3D)





Röntgen



Courtesy GE

Index

CERN & fundamental research characteristics

Research results for health that strongly impacted society

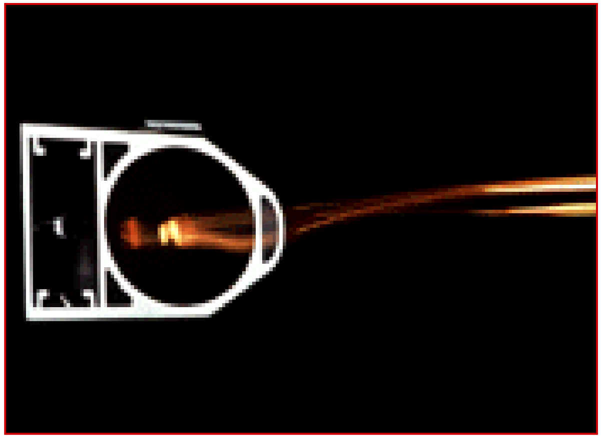
How research can help society meet challenges ahead

- Health
- Molecular biology

How can current physics research programme benefit society?

CERN tenders European industry for the procurement of all the main elements (or their constituents) of the accelerator and an important part of the experiments.

- HEP very challenging requirements can greatly enhanced many different industrial processes
- Industry acquires new technologies and know-how through procurement contract with CERN
- Impact of procurement to industry
- Financial:
  - For 1 Euro invested in purchasing technology goods, more than 3 Euros are generated in companies
- Knowledge transfer:
  - Context: 629 High Tech supplier projects, ~1Bn Euros, 178 survey respondents, No companies with orders < 20 kEuros):
- Results:
  - 38% developed new products
  - 17% opened a new market
  - 14% started a new business unit



Vacuum chamber

Hood clamshell tool in elastomer

Example of a new product developped at CERN to detect Leaks in vacuum, used by the food processing industry

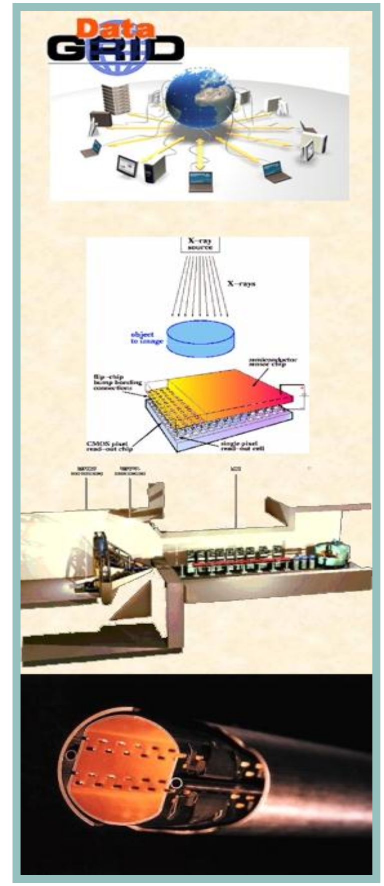
How can current physics research programme benefit society (2)?

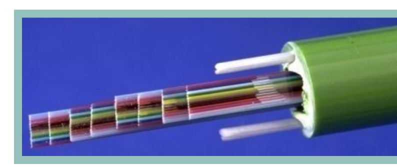
The LHC with its extremely challenging operational conditions has been the source of many new technical innovations and has pushed many detector technologies to their limits.

- Particle physics today has an extensive portfolio of generic and well established detector technologies covering many different technology domains such as photodetectors, gaseous detectors, solid state detectors, scintillators, related readout electronics and data processing.
- HEP portfolio matches multiple product needs in many applied physics and industrial application domains such as medical imaging, life science, homeland security and others.
- Whereas particle detectors for HEP have to meet best possible performance at affordable costs, products from industry have to meet advertised features and customers' needs using robust and proven technologies at the lowest possible production costs resulting in two different technology transfer schemes:
  - New products / applications: PET scanners, World Wide Web
  - New technology in existing industrial products (illustration in the following slides):
    - Super-conducting technologies to reduce device size and energy consumption
    - Very fast counting and very sensitive micro-electronics to enhance device performances

Potential of CERN technologies in non-HEP application domains

		Detectors	Electronics	IT	Accelerator	Magnets	Material Mechanics	Vacuum Technology	Cryogenics
Health & Lifesc.	Detectors	✓	✓	✓					
	Electronics		✓	✓					
	Therapy / Isotopes				✓	✓	✓	✓	✓
Energy & Environment	Energy Storage						✓	✓	✓
	Renewable Energy					✓	✓	✓	
	Thermal Insulation						✓	✓	
	Nuclear Waste treatment				✓	✓	✓	✓	✓
Eng.	Industrial processes				✓	✓	✓	✓	✓





Index

CERN & fundamental research characteristics

Research results for health that strongly impacted society

How research can help society meet challenges ahead

- Health
- Molecular biology

Health: Defeating cancer

Results from the current research programme can contribute significantly to meet this challenge by enabling:

- More compact hadron / proton therapy device using super-conducting technologies and small adjustable (3D) beams:
  - To reduce weight in order to install device on gantry ➔ enhanced flexibility (3D) to optimise beam effect
  - To reduce size in order to lower costs and make device affordable to a larger community
- More accurate and more timely diagnostics device using LHC very front-end electronics for:
  - CT: To reduce doses and enhance contrasts ➔ opportunity for screening
  - Integrated PET-CT: To support 4-D measurement in order to take into account the breathing cycle ➔Better tumour localisation in moving organs ➔ Optimisation of treatment planning
  - Time of Flight PET: To improve image and monitor uptake ➔ localisation of tumour activity
  - PET + MRI: To replace CT ➔ Radiation dose suppression
  - In-beam PET: to monitor on-line the dose deposited and provide feedback data to therapy device

Super-conducting cyclotron directly installed on a Proton Gantry

Standard cyclotron: 200 Tons, 230 MeV protons, 3 T

MIT is designing a super-conducting Nb3Sn synchrocyclotron, 9Tesla, 250 MeV protons, pulsed bunches, cryogen free (Cryocoolers), weight < 35 Tons on a gantry

Standard gantry characteristics: > 100Tons, 10m diameter

LHC detector technologies and electronics can help Health

What the LHC needs

Radiation hard, fast and high precision measurement of:

- Energy
- Momentum
- Time

Detector & electronic technologies

	Examples
Solid State detectors	***Microstrip*** ***Pixel*** ***A-Si:H***
Gaseous detectors	***MWPC*** ***FGLD*** ***GEM***
Calorimeter	***Scintillating crystals*** ***Scintillating fibers***
Photo detectors	***HPD's*** ***Pixel*** ***SiPM/SPAD***
Readout electronics	***Single photon counting*** ***HPTDC timing*** ***Discriminators***

Applications in Medical and Molecular Imaging:

- PET
- CT
- X-Ray
- SPECT
- MRI

Performance

- High sensitivity for small tumor detection
- High specificity to avoid unnecessary biopsies and wrong diagnostics
- Ultra fast Signal Analysis
- High Spatial Resolution

but also

- Compactness
- Low cost
- Mature technology
- Liability
- Flexibility in use

LHC electronics for spectral CT to enhance contrast and reduce dose

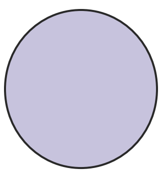
A paradigm shift: from current mode CT to counting mode CT

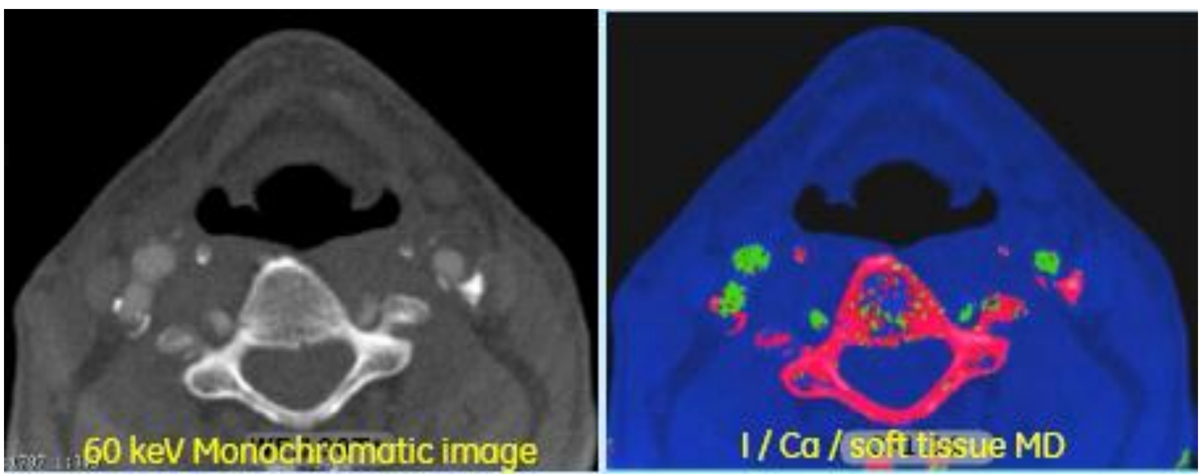
Current mode CT

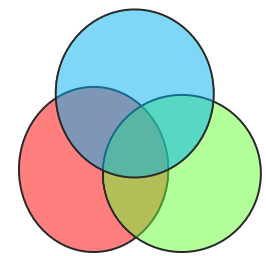
- Limited contrast
- No information on X-ray energy
- High dose
  - → Restricted use for screening
  - → Limited access to preventive health care market

Counting mode CT

- High contrast
- Tissue decomposition through colour mode
- Up to 10 times lower dose
  - → Opportunity for screening
  - → Access to preventive health care







Courtesy GE   Courtesy Rabin Medical Center, Israel

Integrated PET-CT for 4-D functional imaging

PET-CT integration to multimodal system

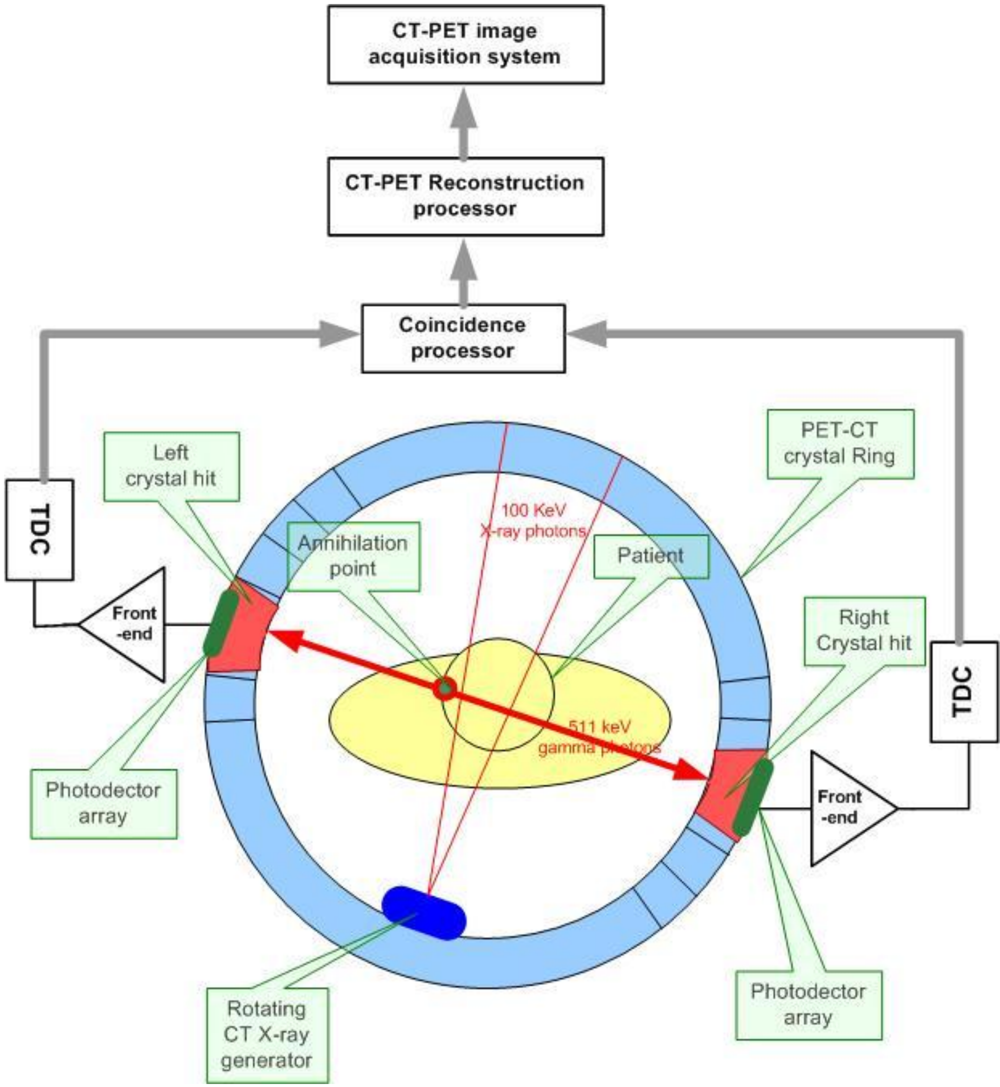
- PET and CT event data acquisition using the same detector heads

3-D and time synchronization

- PET and CT events time stamped throughout the examination
- 3-D image reconstruction over examination time

Advantages

- Morphological and functional images are fused taking into account the breathing cycle
- Enriched image information through merging morphological and functional images in the same reference system
- Reduced complexity in cross-modality calibration



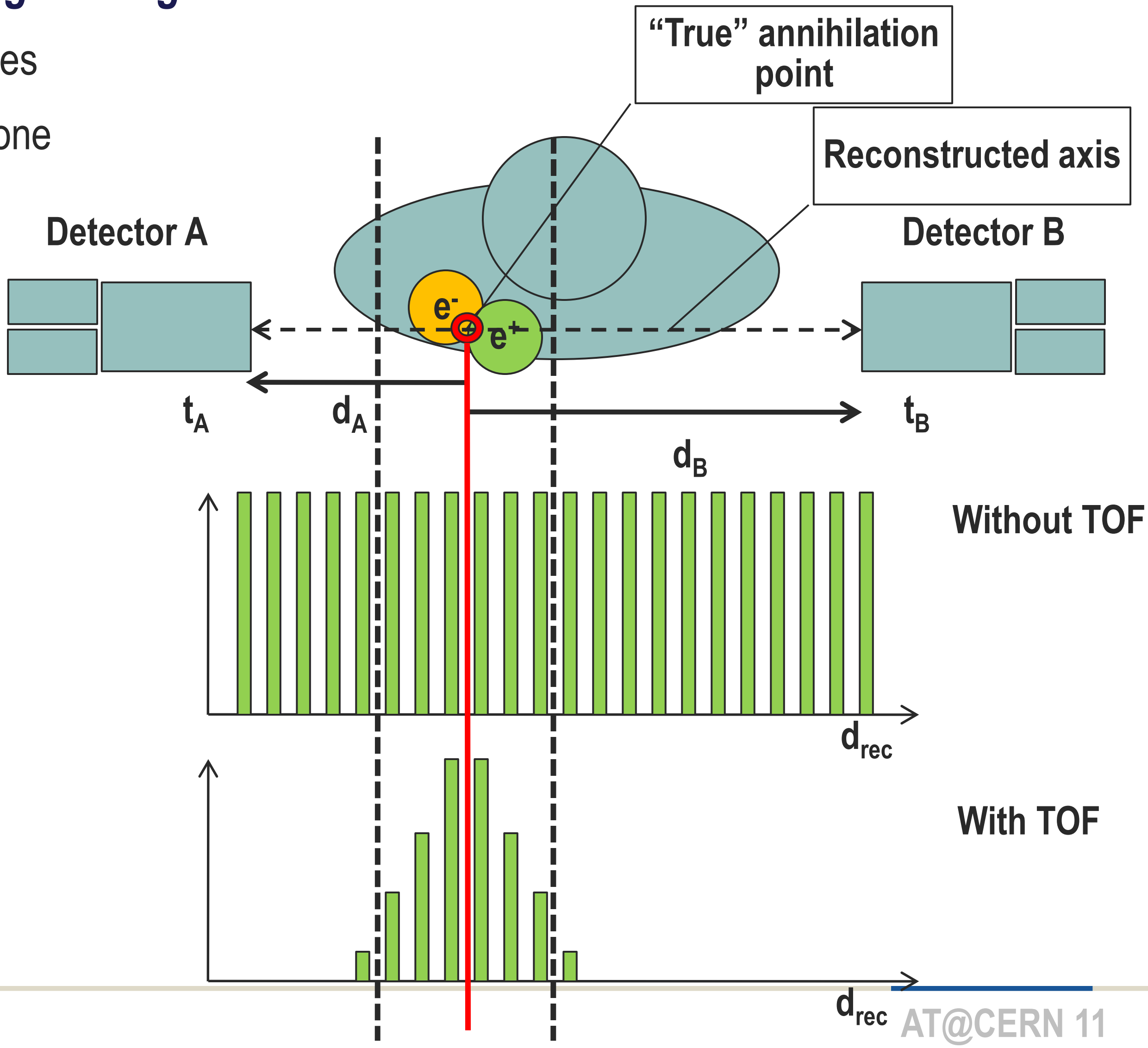
Time Of Flight PET to improve image quality

Improve image quality through background reduction:

- Discriminate random coincidences
- Exclude events outside target zone

Arrival time difference of photons $\Delta t = t_A - t_B$ depends on position of annihilation point

TOF: use time stamp information of incident photons to reconstruct annihilation point and to define target zone



Advantages:

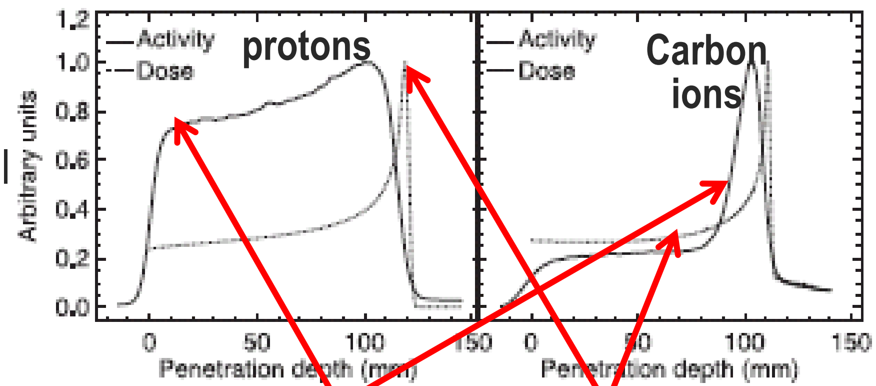
- Improved contrast
- Shorter reconstruction time
- Less dose for patients

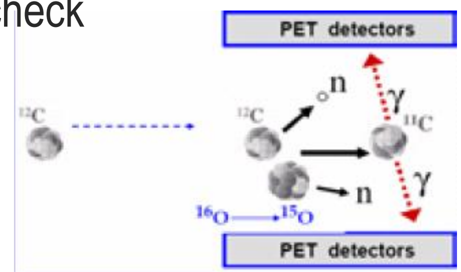
In beam Time Of Flight PET for treatment planning and monitoring

Courtesy K.Parodi

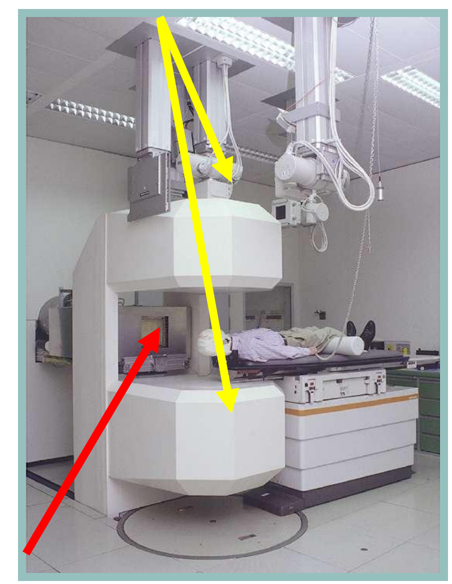
Utilisation of in-beam TOF PET in hadron therapy facilities to monitor treatment online

- Carbon ion beam will induce ^{11}C after collision with cell DNA
- ^{11}C is a β^+ emitter which can be used for online PET imaging
- ^{11}C activity profile correlated with dose profile: measure β^+ profile to reconstruct "true" dose profile and check against planning





PET Camera



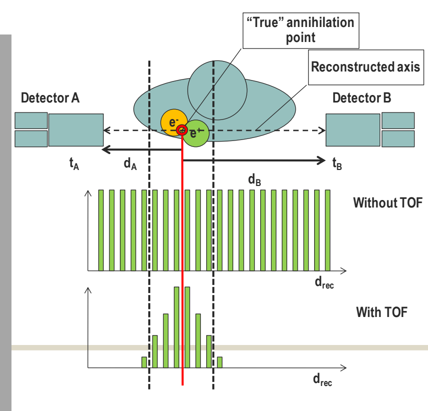
Carbon Beam

In beam-PET offers a unique tool to control the precision of the irradiation profile as well as the treatment plan in real-time

Time Of Flight PET:

- Reduce background
- Minimize time to reconstruct the data

LHC detector front-end electronics can open the path to industrial solutions:
- **Crystal readout with APD's and SiPMs**
- **Ultrafast counting electronics**



PET – MRI to substantially reduce dose delivered to patient

"The development of combined PET/CT scanners has allowed major expansion of molecular imaging," Michael Welch, co-director of the Division of Radiological Sciences at the Washington University School of Medicine (St Louis)

- PET scanning requires a very small dose for patient

But: *the addition of CT to PET means a substantial increased radiation dose for the patient.*

Solution*:* ***Replace CT with MRI***

- No additional radiation dose to patient
- High contrast morphological information

Challenge

- Development of PET electronics compatible with high magnetic field of MRI

LHC detector front-end electronic can open the path to an industrial solution

- Crystal Read-out: APD, SiPM

PET Functional imaging: PET - MRI

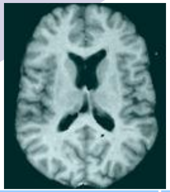
"The development of combined PET/CT scanners has allowed major expansion of molecular imaging," Michael Welch, co-director of the Division of Radiological Sciences at the Washington University School of Medicine (St Louis)

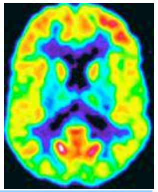
Functional & morphological imaging

Low dose rate for PET

High dose rate for CT

PET/CT mostly not really simultaneous





Key parameter	MRI	PET
Anatomical detail	Excellent	Poor
Spatial resolution	Excellent	Compromised
Clinical penetration	Excellent	Limited
Dose rate	Excellent	low
Sensitivity	Poor	Excellent
Molecular imaging	Limited	excellent

LHC detector front-end electronics can open the path to industrial solutions:
- **Crystal readout with APD's and SiPMs**
- **Compatible with high magnetic fields in MRI**

Courtesy U. Pietrzyk, FZJue;ich

ClearPEM-Sonic: Introduction

High risk of breast cancer at some point of life, 2nd cause of cancer death amongst women

- Very good survival rates if detected at an early stage

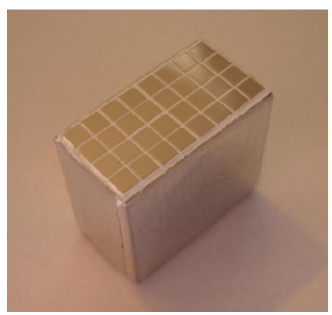
But available techniques (Xray, US, MRI, wholebody PET/CT) all have disadvantages

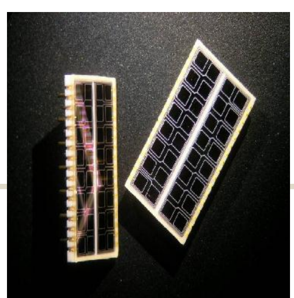
Room for another technique, ClearPEM-Sonic, that combines:

- ClearPEM, a dedicated mammography PET → METABOLIC information
- SupersonicImagine Aixplorer,
  - a 3D ultrasound and elastography system → MORPHOLOGIC and STRUCTURAL information

…. an imaging modality that improves the quality of breast cancer diagnosis

ClearPEM-Sonic: the machine





A dedicated mammography PET:

- Breast exams with patient in prone position
- Plates rotate around the breast
- Plates can be rotated for axillary exams

Two prototypes in operation

- ICNAS – Coimbra (ClearPEM)
- Hopital Nord – Marseille (ClearPEM-Sonic)

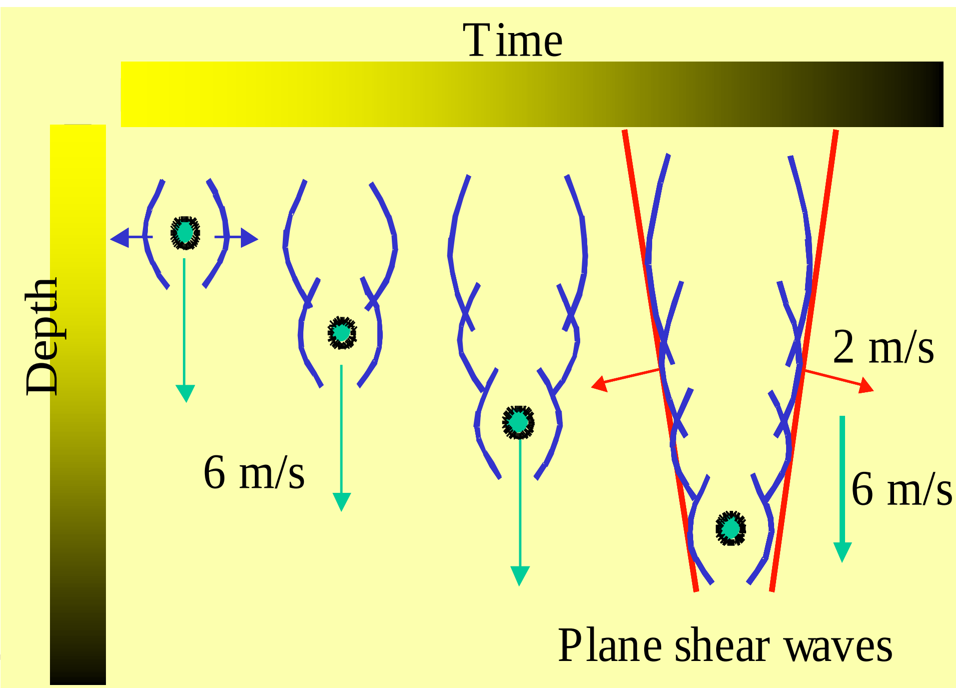
Technology

- 6144 LYSO:Ce crystals in 192 matrices
- APD readout on both sides of each crustal
- Fast Front-End readout with dedicated ASICs

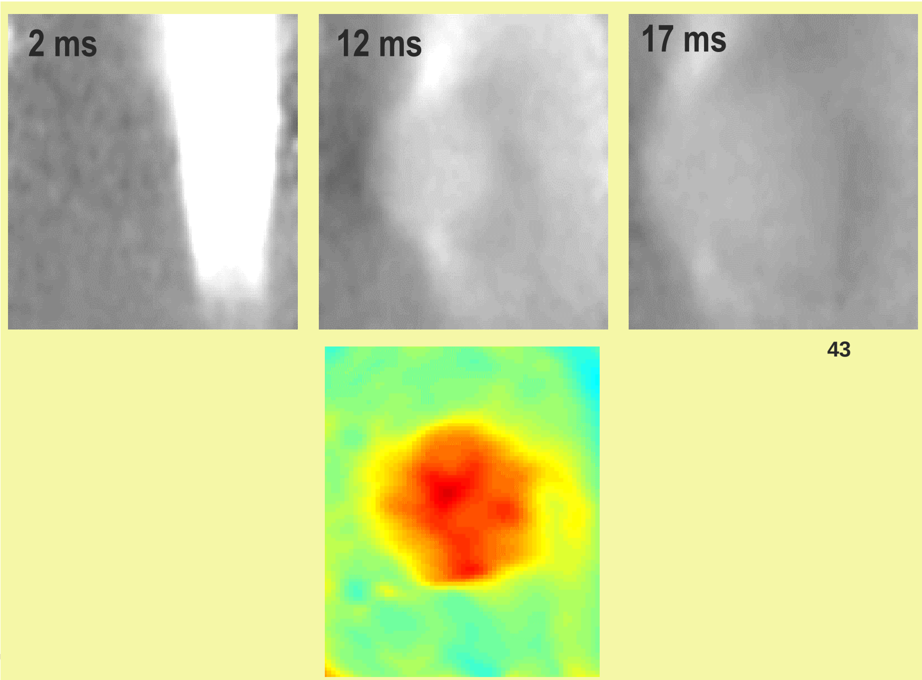
US system: Elastography Principle

- injects a focalized beam that moves with supersonic speed through the tissue
- this long focused pulse creates Dynamic Radiation Force that generates transient Shear Waves
- this Shear Wave front is altered by different tissue stiffnesses
- this information is captured with Ultrafast ™ imaging

→ user-independent, real-time, quantitative method

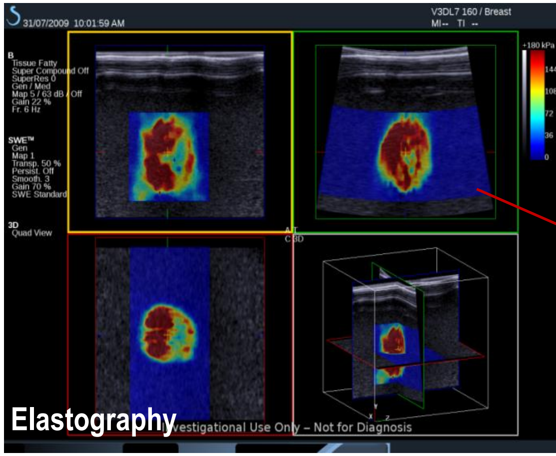


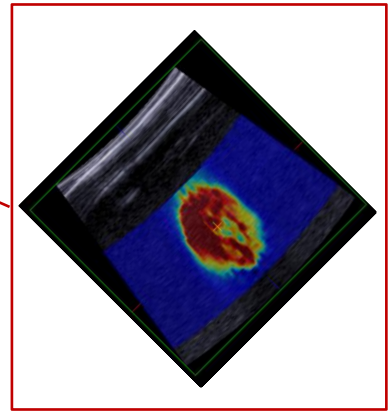
The principle of elastography

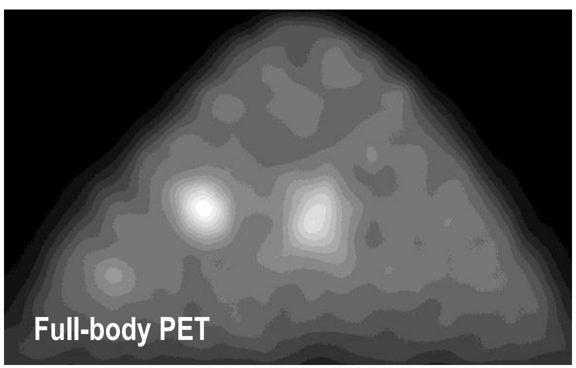


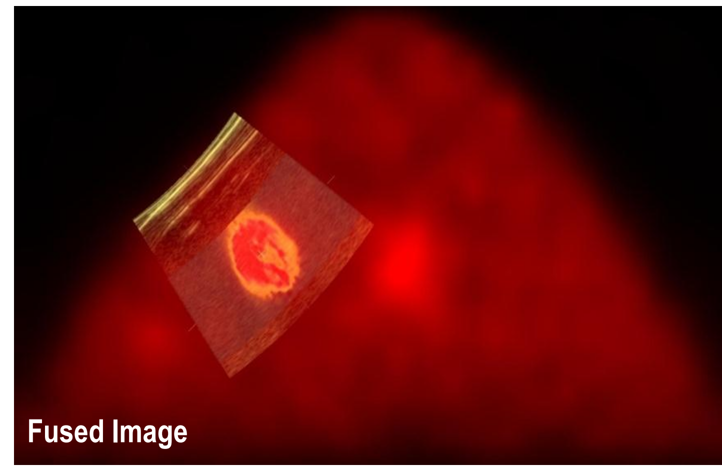
Shearwave propagation around a lesion

ClearPEM-Sonic: Proof of Concept









- Agar-Agar / Gelatin phantom with lesions (developed by Dang JUN from Brussels University, see his talk)
- First image taken with SSI AIXplorer in elastographic mode, second image taken with full-body PET (IPO)

→ Reconstructed images (courtesy Dang JUN) show it is possible to match both images using fiducial markers and the magnetic positioning system

Index

CERN & fundamental research characteristics

Research results for health that strongly impacted society

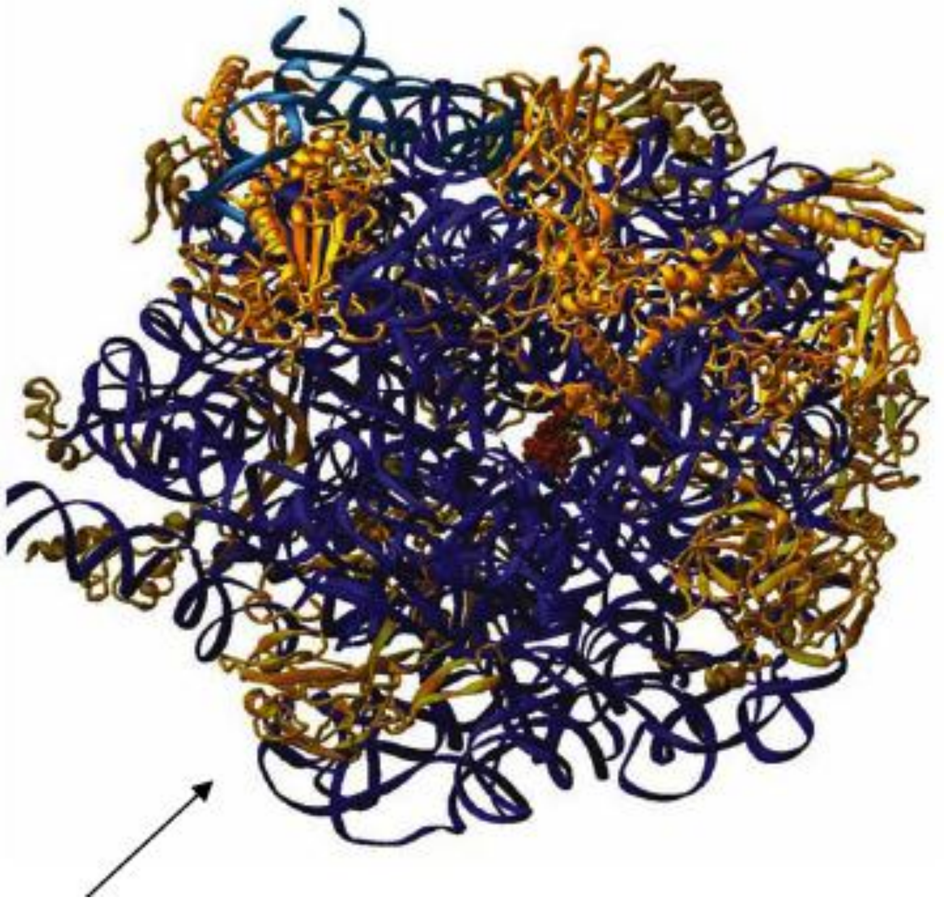
How research can help society meet challenges ahead

- Health
- Molecular biology

Advanced accelerator and detector techniques to probe molecules in cells

Molecular biology is in great need of technologies from fundamental research to unravel the mechanisms of life

- Advanced simulation tools to build an accurate model of a living cell
- Synchrotron light sources (accelerators) to image complex molecules
- Very fast, very sensitive read-out electronics to capture intra and inter cellular ions and molecule exchanges using fluorescence imaging techniques
- Complex analysis techniques to exploit the huge amount of data generated by micro-arrays assays



The intrinsic structure of a complex protein molecule has been determined by reconstructing scattered synchrotron radiations (Spring 8, Japan)

Applications of fast counting read-out electronics to spectroscopic imaging

Single photon counting electronics allows extremely low dose rate imaging and access to spectroscopic information enabling new imaging applications

Life Science

Time resolved diffraction measurements at synchrotrons with unprecedented dynamic range and speed

Medicine

First experiments in spectral X-ray imaging

- Starting with small animal CT
- Aiming for CT for preclinical studies in the coming years
- Ultimate aim is colour X-ray CT for mammography and whole-body

Material Science

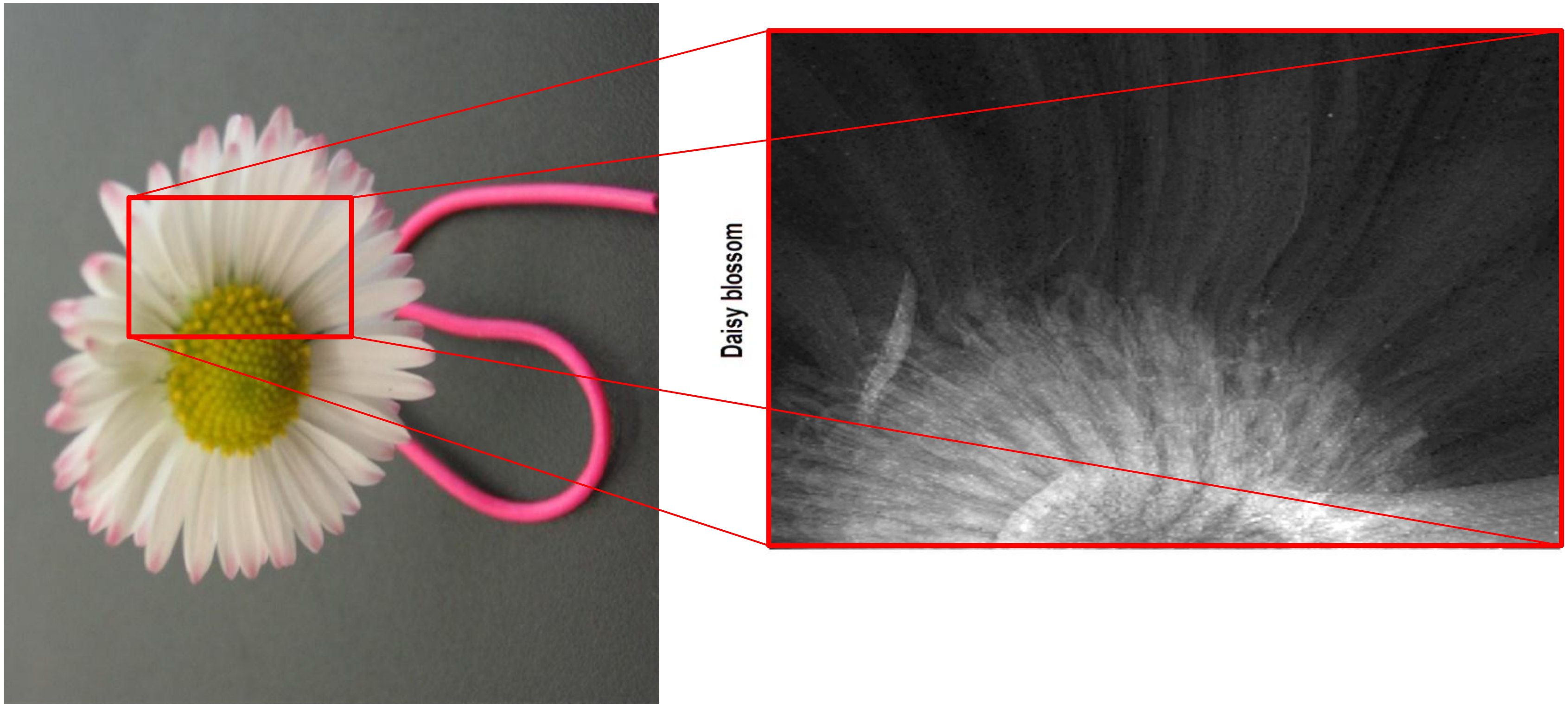
Improved thickness gauging and material determination

Environmental Monitoring

Radiation monitoring instruments (area radiation monitoring, object monitoring, personal dosimetry)

High-resolution X-ray Radiography

- **Image of a daisy (almost transparent to X-rays)**

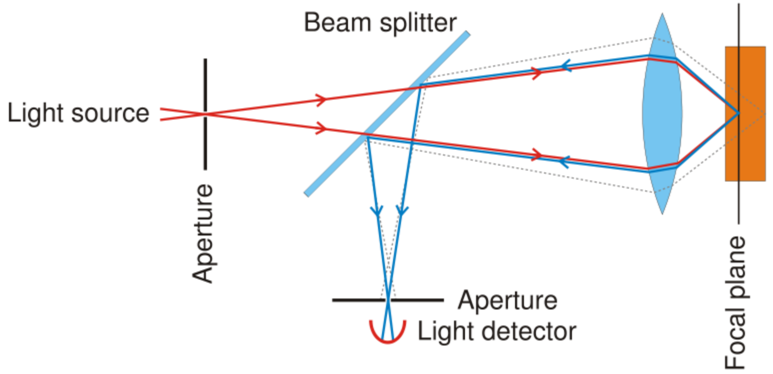


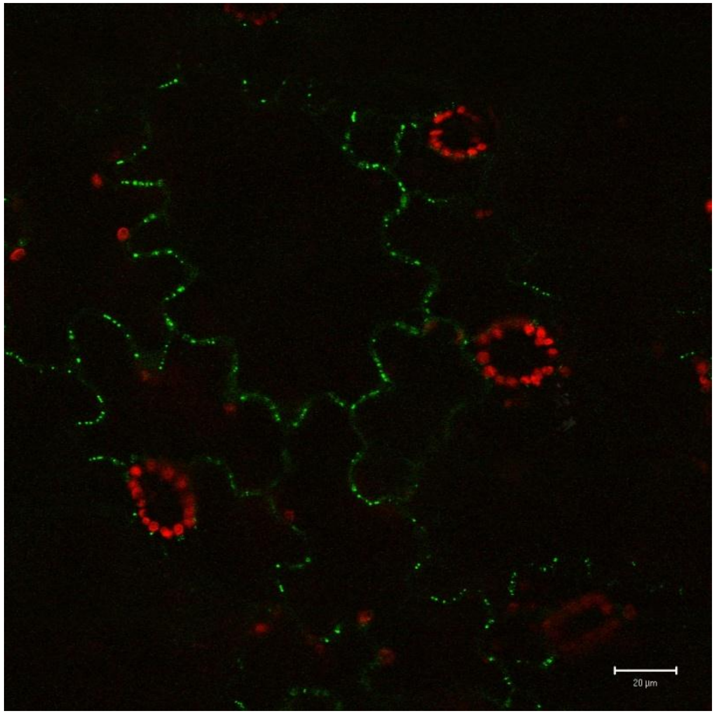
Polychromatic source is used. Single photon counting permits ultra-high contrast imaging after correction for spectral hardening
Institute of Experimental and Applied Physics, Prague

Confocal laser scanning microscope

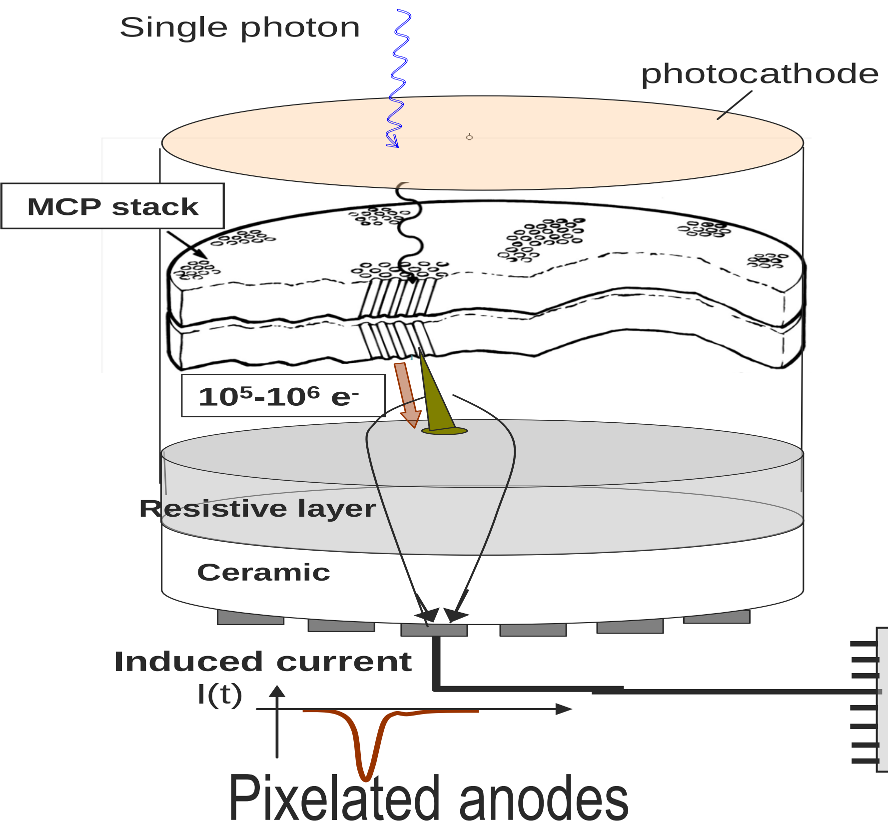
A laser beam passes through a light source aperture and then is focused by an objective lens into a small (ideally diffraction limited) focal volume within a fluorescent specimen. A mixture of emitted fluorescent light as well as reflected laser light from the illuminated spot is then recollected by the objective lens.

A beam splitter separates the light mixture by allowing only the laser light to pass through and reflecting the fluorescent light into the detection apparatus. After passing a pinhole, the fluorescent light is detected by a photodetection device (a photomultiplier tube (PMT) or avalanche photodiode), transforming the light signal into an electrical one that is recorded by a computer.

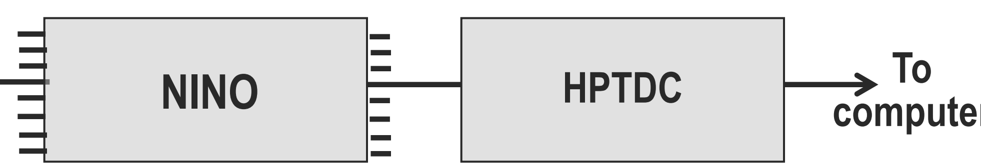




Single photon counting and imaging with microchannel plate



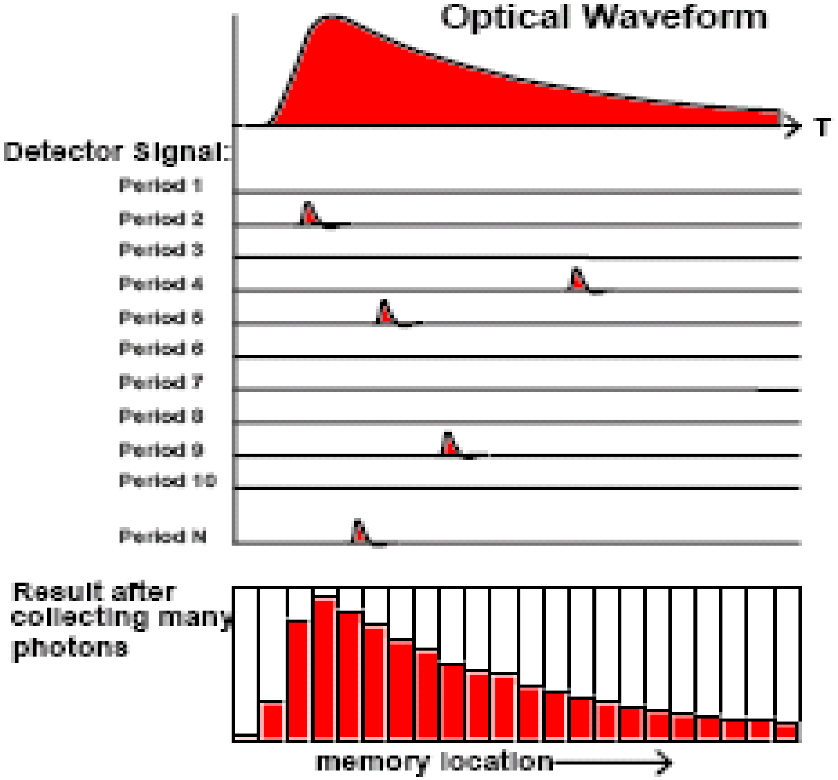
- The front end NINO read out a pixelated micro channel plate
- Signal from NINO are “time stamped” by the HPTDC
- Following signal processing is performed in FPGA by user



Molecular imaging: Fluorescence Lifetime Imaging

Fluorescence imaging

- Each visible photon quanta is detected and counted in a pixel or correlated with its time stamp



Single quanta detectors for visible photon

- Photomultiplier
- Microchannel plate
- Hybrid Photo detector
- Single Photon Avalanche Diode (SPAD)

Benefits

- Very sensitive to various interactions between fluorescent molecules and cell environment
- Ultra-high Time Resolution - 25 ps
- Ultra-High Sensitivity - down to the single photon level

Conclusions

Basic research has a strong impact on technology developments and innovation

Technology developed for science have major repercussions on the global community

Technology developed for science is a source for Industry that leads to important business prospects

Fundamental science accelerates the industrial process and improves daily life

Many issues, including funding are limiting the impact of public research to industry and society