Erice International School of Scientific Journalism and Communication

New Particle Imaging Methods for Advanced Medical Diagnostics and Therapy

G. Cuttone

INFN-LNS

President of the INFN National Committee for Technological and Interdisciplinary Research (CSN5).





INFN Interdisciplinary Research Fields Hadrontherapy Dosimetry Imaging **Advanced Imaging Detectors for medical physics Cultural Heritage BNCT** Radiobiology

These activities are funded in the CSN5 and in strategic project INFN-MED In my presentation just a short view of the activities related to Imaging and Therapy.

. . . .

Why clinical hadron beams?



In 90' years INFN supported TERA in R&D project.

INFN, in collaboration with University of Catania, realized in its laboratory (Lab. Naz. del Sud) the first Italian protontherapy facility.

INFN has UNIQUE capability in Italy in accelerators development. In 2006 an agreement with IBA has been signed for selling an innovative Superconductin Cyclotron for hadrontherapy.

Considering its particular features, INFN was involved in CNAO to guarantee the necessary expertise.

In 2005 INFN was encharged by Health Minister to produce a document about protontherapy in our country.

In 2008 A project for a new treatment planning system started in collaboration with IBA/CMS/ELEKTA



5

Bending limit	K=800
Focusing limit	Kfoc=200
Pole radius	90 cm
Yoke outer radius	190.3 cm
Yoke full height	286 cm
Total weight	176 tons
Min-Max field	2.2-4.8 Tes
Main coil At	6.5 10 ⁶
Sectors	3
Min. hill gap	8.6 cm
Max valley gap	91.6 cm
Trim coi l s	20
Dees	3
RF range	15-48 MHz
Oper. Harmonics	1,2,3,4
Peak dee voltage	100 KV

LNS Accelerator Layout

Ocular Protontherapy

INFN

Unique Italian Facility

CATANA

Patient Distribution by Origin Region

Total number of patients : 220 Since feb 2002



SURVAIVAL RESULTS		
PatientsTotal Number (April 2010)	220	
Dead patients	4	
	Metastatis	3
	Other	1
Eye retention rate	95 %	
TOTAL SURVIVAL	98 %	
LOCAL CONTROL	95 %	

C400: a novel approach to hadrontherapy

Based on the solid experience built in proton and carbon therapy, INFN with IBA and JINR is proposing today a cyclotron based solution for carbon beam therapy

We are collaborating with IBA-Elekta-CMS in the development of a new, improved treatment planning for carbon therapy

IBA is finalizing finalizing the agreement with Archade to install the prototype of C400 Carbon therapy system in Caen

Engineering view of the C400 MeV/u cyclotron





The C400 cyclotron design

Superconducting isochronous cyclotron, accelerating Q/ M = 1/ 2 ions to 400 MeV/ U (H2 + (up to 265 MeV/ u), Alphas, Li6 3+, B10 5+, C12 6+, N14 7+, 016 8+, Ne20 10+)

Design very similar to IBA PT cyclotron (15 units built) and INFN K800, but with higher magnetic field thanks to superconducting coils, and increased diameter (6.3 m)

The proton-carbon facility





<u>The TPS project of INFN</u> for the development of new Treatment Planning Systems in hadron therapy with light ion beams

Aim and features of the INFN project

- Contribute to the development of innovative Treatment Planning Systems for therapy with ion beams (in particular ¹²C, but not exclusively) for active voxel scanning applications
- To produce a well defined, certified and ready-touse deliverable in collaboration with an industrial partner → IBA (through associated Elekta-CMS)
- Collaboration with CNAO in Italy for testing
- Scientific collaboration with other European Institutes for aspects concerning nuclear physics and radiobiology

Areas of relevant competences within INFN

- Nuclear Physics
- MC simulation
- Optimization algorithms
- Experimental Radiobiology
- Monitoring "in beam"

these are the 5 tasks of the INFN TPS project

Cross section measurements: activity at INFN-LNS

We already measured the ¹²C fragmentation on ¹⁹⁷Au and ¹²C targets with 62 AMeV CS beams at LNS-INFN, In 2009 we plan to use different beams up to 80 AMeV.





The ALADiN Spectrometer



The ALADIN Recipes

INTERNATIONAL SCENARIO

- IAEA Benchmark of Spallation Models (<u>Detlef Filges</u>, Forschungszentrum Jülich, Germany, <u>Sylvie Leray</u>, CEA Saclay, France, <u>Gunter Mank</u>, IAEA Vienna, Austria, <u>Yair Yariv</u>, Soreq NRC, Israel, <u>Alberto Mengoni</u>, IAEA Vienna, Austria)
- IAEA "Heavy Charged Particle Interaction Data for Radiotherapy" (G. Cuttone INFN, O.Jaekel DKFZ, A. Ferrari CERN, A. Heikkinen Univ. of Helsinki, T. Lomax PSI, H. Palmans NPL, H.Paganetti. MGH, M.C. Morone INFN & Univ. of Rome Tor Vergata, M. Quesada Sevilla Univ., R. CapoteNoy & S. Vatnisky IAEA Vienna,)
- ESA SEENOTC (Energetic particle radiation and its effects on systems, payloads and humans) Field of Interest: Ion fragmentation (50 AMeV → 1000 AMeV)

The task about PET on line: Stringent necessity of monitoring

The higher physical selectivity of ion therapy demands higher precision in the monitoring of the applied treatment due to:

- fractioned therapy
- shifts of the patient
- local tissue reduction

For these reasons in vivo information on the range of ions are desirable, but the complete stopping of the ions in patient prevents the application of electronic portal imaging methods as used in conventional radiotherapy.

Possibilities:

- radiographic imaging of high energy transmitted protons prior to therapeutic irradiation (hadron CT)
- In-beam PET

β+- emitter target and projectile fragments:

- Protons:
 - ¹⁶O (p,n) ¹⁵O ¹²C (p,n) ¹¹C *T*^½₁₅₋₀=121.8 s *T* ^½ _{11-C} =1222.8 s
 - 15-20 MeV threshold for p-induced nuclear reactions that cause poor spatial correlation between β⁺-activity and dose depth profile
- Carbon:

•

- X (¹²C, ¹¹C+n) X X (¹²C, ¹⁰C+2n) X ¹⁶O (¹²C, X) ¹⁵O+n ¹²C (¹²C, X) ¹¹C +n $T^{\frac{12}{2}}$ 10-C =19.3 s
- Superior biological effectiveness



The INFN experience: DOPET



LYSO crystal matrix, 21 x 21 pixels 2.152 mm x 2.152 mm each (Hilger Crystals)
Crystal thickness: 18 mm
64-anode PMT (Hamamatsu)

•"multiplexed" read-out electronics: 64-inputs/4 outputs

•Two planar heads, each with an active area of 45 mm × 45 mm

•Distance between the heads: 7+7 cm

Nominal energy: 62 MeV Final collimator: 25 mm Ø Full energy Dose: 30Gy peak T-irr= 20sec. T-acquis = 20sec

The experiments on homogeneous phantoms

The feasibility of range monitoring



DoPET results

Unfolding

F. Attanasi, N. Belcari, M. Camarda, V. Rosso, S. Vecchio, G.A.P. Cirrone, G. Cuttone, A. Del Guerra, F. Di Rosa, N. Lanconelli, G. Russo Experimental validation of the filtering approach for dose monitoring in proton therapy at low energy Physica Medica -European Journal of Medical Physics, *24/2*, (2008), 102-106 doi:10.1016/j.ejmp.2008.03.001.



Reconstructed activity (*) in comparison with the dose (dash-dot line) and the filtered dose (solid red line)

Resolution of air gaps in PMMA phantoms within the irradiation field

PMMA phantom with 0.5 cm Air_Gap at 2 cm depth;



- Phantom irradiation:
 - Bragg peak dose: 30 Gy
 - Irradiation time: 18 s;
- •Beam cross sention: 2.5 cm Ø;
- Acquisition time: 20 min;



Resolution of air gaps in PMMA phantoms within the irradiation field

 \cdot Final three holes collimator: 0.5 cm Ø each; _{Activity distribution in the central slice}







Phantom irradiation:

- Bragg peak dose: 30 Gy
- Irradiation time: 18 s;
- Beam cross sention: 2.5 cm Ø;
- Acquisition time: 20 m;







- Monoenergetic irradiation:
 - Bragg peak dose: 30 Gy;
 - Irradiation time: 18 s;
- Beam cross sention: 2.5 cm Ø;
- Acquisition time: 20 min;







Summary of main results

Homogeneous PMMA phantoms, SOBP irradiation

- 1) Capability of detecting difference in distal fall at mm level.
- 2) Capability of detecting small air cavities
- 3) Capability of reconstructing contributions of activity from different isotopes:
 - a) ad hoc slab phantom to generate only C (using PE. PMMA has both O and C)
 - b) other phantom PMMA+bone. Bone generates K which is detected as a contribution added to O

Software goals

- Improvement of the algorithm for the 3D reconstruction of the activity distribution to achieve a better image quality
- Improvement of the system model
- Realization of an unfolding filter to extract the Dose
- Inverse filter to achieve dose localization:

InvFilt * Att = Dose.

Hardware goals

 Design, assembly and test of improved detection modules and readout



rison of two dedicated "in beam" PET



⁴ BASTEI (beta activity measurements at the Therapy with Energetic ions) is in use at GSI.

2 heads 42x21 cm2

8x8 BGO christals: 6.7x6.7x20mm3

A cylindrical PMMA phantom (7cm diameter, 7cm length) was irradiated with 3 monoenergetic 12C beams (108.53 112.60 116.57 AMeV). A square section beam of 28mm in side was adopted and a total dose of 60Gy was delivered for each energy. The acquisition time was set at ~30 minutes for both PET systems.

Preliminary

	Simu	Itaneous	irradiations	with	12C
--	------	----------	--------------	------	-----

Energy	[AMeV]	108.53	112.60	116.57
Range	[mm]	21.9	23.6	25.3





Recostructed on p5











201.1 MeV protons at LLMUC 236 µm strip pitch Si telescope with CsI (TI) calorimeter

Thomson back-scattering X-ray source Quasi-monochromatic beam

 $E_X = 20 \div 800 \, keV$



Tuneable X-ray radiation source based on Thomson Scattering



BEATS: FIELD OF APPLICATIONS

- 1.Mammography
- 2.Low-dose lung CT
- **3. Fissile Materials Identification**
- 4.Cristallography
- 5. 3D Microdensitometry for cultural Heritage

Source Description



- Geometry
 - Source Size : 13 μm
 - Divergency: 5 mrad
 - Source-Detector Distance ~ 10m
 - Illuminated Area: Ø=5cm
- Flux
 - 10¹⁰ photons/s
- Time Structure
 - Bunch lenght 6 ps, rep. rate 10 Hz
- Space Consistency
- Quasi-monochromatic Spectra with harmonic

Brookhaven National Laboratory

Accelerator Test Facility

Dedicated Beam line for Thomson scattering Preliminary Imaging with TS

Phase Contrast?Dual edge imaging?







Figure 1. Top view of the Compton chamber





Compton Chamber

Phantom



Images of the phantom



Single shot



Nylon wire (150 micron diamete



Sum of 20 shots -bg



PET wire (500 micron)

PMMA wire (1mm)

Simulation for PMMA 1000 micron



PSF of the detector 200 μ m

Image of the PMMA wire





Count: 2436 Mean: 240.107 StdDev: 22.028 Bins: 256 317.850 Min: 156 Max: 317.850 Mode: 247.357 (38) Bin Width: 0.632

> $\Delta N/N = 10\%$ More than the expected C_p

Bg F=240

Profile (mean on 50 columns)



 $C_A = (F-V)/F=0.54$ absorption V=109



Single Shot 20 psec.

You can clear see the phase contrast effect, mainly on the back of the wasp

The SPES-BNCT project goals

- a. The construction of an accelerator-based intense thermal neutron beam demonstration facility, aimed at the skin melanoma tumor treatment through a combined Boron Neutron Capture plus Photodynamic (BNCT+PDT) therapy approach.
- b. The development of a new dosimetric system based on microdosimetric detectors for on-line biological dose monitoring in tumour & health tissues.
- c. The development and test of new boron carriers having a combined photodynamic effectiveness.

The BNCT irradiation facility concept

SPES (SELECTIVE PRODUCTION OF LAR SPECIES)





Juan Esposito "The SPES-BNCT project of INFN Legnaro labs." Seminario di Discussione "Sorgenti di Neutroni e loro Applicazioni in ambito INFN", Legnaro, Nov. 17-18-19, 2009

TRIPS (TRasco Intense Proton Source) built at LNS currently operative



Juan Esposito "The SPES-BNCT project of INFN Legnaro labs." Seminario di Discussione "Sorgenti di Neutroni e loro Applicazioni in ambito INFN", Legnaro, Nov. 17-18-19, 2009

The SPES-BNCT Proton driver ready for RF high power tests



Juan Esposito "The SPES-BNCT project of INFN Legnaro labs." Seminario di Discussione "Sorgenti di Neutroni e loro Applicazioni in ambito INFN", Legnaro, Nov. 17-18-19, 2009 The experimental evidence of the feasibility of an accelerator-based thermal neutron source for BNCT applications on skin melanomas based on TRASCO RFQ



Characterisation of an accelerator-based neutron source for BNCT versus beam energy, S. Agosteo et al., Nucl. Instr. Meth. A, Volume 476, Issues 1-2, 1 January 2002, Pages 106-112

An Accelerator-Based Source of Thermal Neutrons for BNCT of Skin Melanoma: Status of the Project, S. Agosteo et al. - Proc. of the 7th Int. Conf. on Applications of Nuclear Techniques: Nuclear and Atomic Industrial & Analytical Applications, Crete Greece, 17 –23 June 2001, G. Vourvopoulos, Ed., Produced by Gray Spichiger, Western Kentucky University, Kentucky, USA, Published on CD ROM.

ECORAD: Ecography+SPET





Preliminary results of slant hole collimator tomography

ECORAD

Source position	Planar	Axial
@ 1 cm	3.0 mm	7 mm
@ 3 cm	5.7 mm	12 mm
@ 5 cm	7.0 mm	15 mm

Reconstructed coronal slices:





M.C. Geant4 simulation Scintillation light transport is also simulated INFN Bologna

- Z linearity is strongly dependent on the detector position linearity
- Axial spatial resolution is two times worst than planar resolution
- Spatial resolution is dominated by collimator geometry

ECORAD perspectives

- ECORAD is the first diagnostic imager integrating an Ultra sound (US) probe with a Gamma camera with very high spatial resolution.
- ECORAD can be used in the **future for small animal imaging** due to its very high resolution power.
- ECORAD can **improve clinical sensitivity**^{**} of any diagnosis where a US imaging is the gold standard and an ancillary technique for many others.
- Some USA University Hospitals are interested to test or implement a copy of ECORAD imager

**clinical Sensitivity = (TP / (TP + FN) TP True Positive Test, FN False Negative Test

The MAGIC-5 Project

Development of models and algorithms for the analysis of distributed medical images

- support the radiologist's diagnosis with Computer-Aided Detection (CAD) algorithms
- improve computational speed, data accessibility and sharing of distributed images
- enable the co-working of medical experts and to allow large-scale statistical analysis

Analysis of Medical Images

- * Mammograms for the early diagnosis of breast cancer (1998 -)
- * Lung CTs for the early diagnosis of lung cancer (2004 -)
- ✤ Brain MRI for the early diagnosis of the Alzheimer's disease (2006 -)







Interdisciplinary know-how •Several techniques developed in High Energy Physics (HEP) and astrophysics experiments are implemented and optimized in medical image analysis to detect very low signal in a noisy background.

•Our past and present activities in HEP and Astrophysics experimentation



- PAMELA Collaboration, An anomalous positron abundance in the cosmic rays with energies 1.5 100 GeV
- NATURE, Vol. 458, 607-609, (2 April 2009) cited 185 times

The MAGIC-5 CAD station for Mammography



- Image Acquisition & **Manipulation (DICOM)**
- Metadata & Diagnosis insertion
- CAD execution

Data storage & retrieve through GRID Services



The MAGIC-5*

- Lung Cancer among top causes of death
- Can screening help?
 If so, Computer Assisted Detection would be useful
- Lung CAD developments with different approaches
 - Region Growing (deterministic)
 - Dot-enhancement / VBNA (deterministic)
 - Virtual Ants (probabilistic, non linear)
 - + neural classifier
- Looking for an industrial partner to turn the prototype into a market product

lung CAD **ANODE09** international competition 3 best scores © **DB MAGIC5** - 50 annotated cases (training) **DB ANODE09** - 5 annotated cases (testing) 1.0 - 50 unknown cases (validation) 0.9 -0.8 0.7 0.6 Sensitivity 0.5 0.4 - V-ANTS 0.3 RG 0.2 VBNA 0.1 0.0 2 0 6 8 FP/scan

*the ITALUNG_CT projects provides CTs and Annotation

MAGIC-5 for the early diagnosis of the Alzheimer's Disease

improved knowledge concerning the pathophysiological mechanisms of neurodegenerative diseases, especially Alzheimer disease, has led to the development of putative treatments which are entering clinical trials"

AUC = 0.93

(M.W.Weiner, MD) 135 Normal subjects (75.5 ± 5.7) y

90 MCI converted to AD in t \approx 2 years

"Application of **Automated Medial Temporal Lobe Atrophy Scale to Alzheimer Disease**" Arch Neur. 2007; 64



247 MCI (75.0 ± 7.0) y

150 AD (76.8 ± 7.3) y

patients

0.9 0.8 (Sensitivity) 0.6 Positive Positive Positive **Frue** 0.3 0.2 0.1 0 0 0.2 0.4 0.6 0.8 False Positive (1-Specificity) MAGIC-5 Arch Neurog. Paper (atlas/visual/HC vol)



85%

Sensitivity = Specificity

84%

(a)

dixit distributed infrastructure X implementing trials

- Web-based Clinical Trial protocol implementation
 - Central server @ INFN, Torino
 - WEB Clients in Hospitals
- Image upload/download
- Automated choice of medical doctors for the diagnosis within the registered pool
- Notification to the selected medical doctors
 & reminders!
- Real time notification of diagnosis
- Online image repository
- In use for the GITIL* clinical trial
- Easily adaptable to other protocols
- Advantages:
 - Simple and easy to use
 - Secure Access from anywhere
 - even more secure if Digital Certificates will be used
 - Trial Protocol must be followed as implemented
 - Much shorter time between upload and diagnosis!

Login form



*Gruppo Italiano per le Terapie Innovative dei Linfomi

AT THE END OF THE HISTORY MANY RESULTS IN THIS FIELD ARE AVAILABLE BUT:

COMMUNICATION OF OUR RESULTS

DISSEMINATION OF OUR RESULTS

BASIC RESEARCH AND HEALTH TECHNOLOGY IMPROVMENT

The lesson: PHYSICS AND HEALTH: A GREAT COLLABORATION.... NOT WELL KNOWN



Thank you for your attention