FLUKA FOR MEDICINE: Application to Cancer Therapy

Rationale for MC in radio- and particle-therapy

- In practice MC codes can be used for:
- startup and commissioning of new facilities
- study of detectors and accelerators
- beamline modeling and generation of TPS input data
- validate analytical TPSs in water/CT systems both for physical and <u>biological</u> aspects
- Prediction/Analysis of in-beam PET application
- Biological calculations for cell survival experiments
- Additional advantage to describe complex geometries (and interfaces between rather different materials!):
- Accurate 3D transport
- Fully detailed description of the patient anatomy
 - \rightarrow CT image converted into a MC geometry

Model challenge: interface to radiobiological model to predict <u>"biological dose"</u> (\rightarrow actual effect) and not only <u>physical dose</u>

FLUKA applicazioni: IORT

First European Workshop on Monte Carlo Treatment Planning Journal of Physics: Conference Series 74 (2007) 012002

IOP Publishing doi:10.1088/1742-6596/74/1/012002

Montecarlo simulation code in optimisation of the **IntraOperative Radiation Therapy treatment with** mobile dedicated accelerator



monitor chambers 100 cm phantom target 10 cm 1-3 cm thickness first disk second disk 12 cm



Alghero, June 2011

FLUKA Applications: Linac Head



Alghero, June 2011

lstituto Nazionale di Fisica Nucleare



FLUKA MONTE CARLO SIMULATION FOR THE LEKSELL GAMMA KNIFE[®] PERFEXIONTM

The Leksell Gamma Knife Perfexion:

The Leksell Gamma Knife Perfexion (LGK-PFX) is a ⁶⁰Co based medical device, manufactured by Elekta AB Instruments Stockholm, Sweden. The It is emplyed in the cure of different brain pathologies: small brain and spinal cord tumors (benign and malignant), blood vessel abnormalities, as well as neurologic problems can be fully treated.

Fabrizio Cappucci INFN, Milan.

The Leksell Gamma Knife Perfexion:



The ionizing gamma radiation is emitted from **192** ⁶⁰Co sources (average activity ~1TBq each).

The sources are arranged on 8 identical sectors of 24 elements.

The sectors can be placed in correspondence of three different collimation set able to focus the gamma rays on a common spot, called the isocenter of the field, having a radial dimension of about 4, 8 and 16 mm respectively.

Fabrizio Cappucci INFN, Milan.

Implementation of the Simulation:



Fabrizio Cappucci

INFN, Milan.

Geometry Modeling;

Source Modeling;

Definition of the bodies;

Definition of the regions (Boolean algebra);

Definition of the materials:

Assignment of the materials to each region.

Simulation Optimization.

FLUKA Geometry Modelization:



Thanks to the collaboration with ELEKTA, which provided, under a confidential agreement the detail of the geometry and all the involved material, has been possible to implement an accurate model for the radiation unit.

~ 1350 bodies

Fabrizio Cappucci INFN, Milan.

Geometry Modelization: Materials



Fabrizio Cappucci INFN, Milan.

Implementation of the Simulation:



Source Modeling;

Definition of the geometries and materials.

Definition of the particle type and energies.

Definition of the starting point of the beam.

Simulation Optimization of the trajectory of the beam.

Fabrizio Cappucci INFN, Milan.

Source Modeling: Geometry and materials



Fabrizio Cappucci INFN, Milan.

Source Modeling:



Implementation of FLUKA External Routine.

- Randomly selects one of 192 available source position;
- Samples the starting point of the beam uniformly inside the source volume;
- Samples the beam trajectories.

Fabrizio Cappucci INFN, Milan.

Relative Output Factors (ROF):

ROFs are the ratio between the dose given by a set of collimators and the dose given by the largest collimators, i.e. the 16 mm.

Collimator size	Elekta ROF	FLUKA ROF	MC Statistical Error	Δ
8 mm	<i>0. 924</i>	0.920	0.84%	0.43%
4 mm	0. 805	0.796	1.21%	1.13%

△ is the percentage difference between the results from Monte Carlo calculation and the Elekta values:

$$\Delta = \left(\frac{Elekta_{ROF}}{FLUKA_{ROF}} - 1\right) \cdot 100\%$$

Fabrizio Cappucci INFN, Milan.

Relative dose distribution:



Fabrizio Cappucci INFN, Milan.

Relative dose profile: 4 mm collimator size.



Radioactive source decay

FLUKA contains data about **decaying schemes of radioactive isotopes**, allowing to select an isotope as radiation source. Complete databases are generated from the data collected **from National Nuclear Data Center** (NNDC) at Brookhaven National Laboratory. Routines are available to discriminate only a component of the emission spectrum, simulating for example only the beta emission and disregarding the gamma one.

Application in nuclear medicine

Application in nuclear medicine

Calculation of absorbed dose at voxel level starting from 3D images of activity distribution (SPECT, PET images)

Simulations in homogeneous water

✓ Simulated ⁹⁹Tc-SPECT of water phantoms (SIMIND code):



 \checkmark Dose calculation: Cylinder + spheres filled with 90 Y



With 10⁹ particles simulated, FLUKA and VOXEL DOSIMETRY results in water agree within 5%

Alghero, June 2011

Rationale for MC in hadron-therapy

- Biological calculations in tumour therapy with ions depend on a precise description of the radiation field.
- In ¹²C ion irradiation, nuclear reactions cause a significant alteration of the radiation field.
- contribution of secondary fragments needs to be taken into account for accurate planning of the physical and biological dose delivery in the scheduled treatment.
- Treatment Planning Systems (TPS) for ion beam therapy essentially use analytical algorithms with input databases for the description of the ion interaction with matter.
- → Monte Carlo codes with sophisticated nuclear models are more efficient (<u>though slower</u>) computational tools to handle the mixed radiation field.

Alghero, June 2011

Nuclear reactions: what really matters?

- Proton therapy (p, E: 10-250 MeV):
 - Reaction cross sections (beam attenuation) +++
 - Elastic cross sections +
 - Particle (p,n,a..) emission + (mostly for background, ++ radiobiology)
 - Positron emitter production + (data available)
- □ Therapy with ions (ions, E: 10-400 MeV/n):
 - Reaction cross sections (beam attenuation) +++
 - Fragment (a included) production +++
 - Particle emission, p +++, others +
 - Positron emitter production +++
- □ Conventional therapy (Y, E: 3-30 MeV)
 - * (γ, x) (particularly (γ, n)) + (mostly for background)

Main FLUKA developments in view of medical applications (and hadron therapy in particular)

- Models for nucleus-nucleus interactions :
- Improvement of models for evaporation/fission/fragmentation used in fragment final de-excitation. Prediction of radionuclide production
- Improvement of dE/dx models (Z²+Z³ corrections, molecular effects, nuclear stopping power)
- Run time application of linear-quadratic models describing radiobiological effects
- Extensions and improvement of neutron library (thermal + ephithermal region)
- Voxel geometry
- Time-varying geometry
- Routines to import CT scans, material/density/composition assignment to CT

Main references to FLUKA in ion-therapy related matters:

- F.Sommerer, K.Parodi, A.Ferrari, K.Poljanc, W.Enghardt and H.Aiginger, Investigating the accuracy of the FLUKA code for transport of therapeutic ion beams in matter, Phys. Med. Biol. 51 (2006) 4385–4398
- 2) K.Parodi, A.Ferrari, F.Sommerer and H.Paganetti, Clinical CT-based calculations of dose and positron emitter distributions in proton therapy using the FLUKA Monte Carlo code, Phys. Med. Biol. 52 (2007) 3369–3387
- 3) A. Mairani, Nucleus-Nucleus Interaction Modelling and Applications in Ion Therapy Treatment Planning, PhD Thesis, Univ. Pavia, 2007
- 4) G.B. et al. (FLUKA collaboration), The FLUKA code and its use in hadron therapy, Il Nuovo Cimento 31C, no. 1 (2008) 69.
- 5) F.Sommerer, F.Cerutti, K.Parodi, A.Ferrari, W.Enghardt and H.Aiginger, In-beam PET monitoring of mono-energetic 160 and 12C beams: experiments and FLUKA simulations for homogeneous targets, Phys. Med. Biol. 54 (2009) 3979-3996
- 6) A.Mairani, S.Brons, A.Fassò, A.Ferrari, M.Krämer, K.Parodi, M.Scholz and F. Sommerer, Monte Carlo based biological calculations in carbon ion therapy: the FLUKA code coupled with the Local Effect Model, submitted to PMB 2010

Nuclear interactions: a nuisance x therapy

- ... easy to switch off in MonteCarlo, a bit less in real life
- ... nice at least I have a good job
- ... Nuclear (and particle) physics cannot be simulated at % level, sometimes you are happy with results within a factor of 2

That's why we always plot results in log-log scales

Playing with a proton beam

Dose vs depth energy deposition in water for a 200 MeV p beam with various approximations for the physical processes taken into account





Alghero, June 2011

G. Battistoni

Bragg peaks vs exp. data: ¹²C @ 270 MeV/n



Bragg peaks vs exp. data: ¹²C @ 270 & 330 MeV/n



G. Battistoni

¹²C Bragg peaks vs exp. data



- Experiment: circles (270 AMeV) and triangles (330 AMeV)
- FLUKA: lines

Sommerer et al: Phys. Med. Biol. 51 2006

Alghero, June 2011

G. Battistoni

Bragg peaks vs exp. data: ²⁰Ne @ 670 MeV/n



From Ref. 1)

Sommerer et al PMB 51 2006



Attenuation of the primaries and fragment spectra obtained by FLUKA for ^{12}C (graphs (a) and (d)), ^{14}N (graphs (b) and (e)) and ^{16}O (graphs (c) and (f)) ions incident in water.

The lower row of graphs refers to projectile fragment spectra. The symbols indicate measured data from Schall (1996). depicts boron, carbon, onitrogen and × indicates oxygen. The simulated boron fragments are depicted by dashed lines, carbon fragments by solid lines and without fragments by dotted lines.

The FLUKA voxel geometry

 It is possible to describe a geometry in terms of "voxels", i.e., tiny parallelepipeds (all of equal size) forming a 3-dimensional grid





Now available the official ICRP Human Phantom ICRP Publication 110: Adult Reference Computational Phantoms - Annals of the ICPR Volume 39 Issue 2



Petoussi-Henss et al, 2002



G. Battistoni

The FLUKA voxel geometry

• The CT scan contains integer values "Hounsfield Unit" reflecting the X-ray attenuation coefficient μ_x

 HU_x = 1000 $(\mu_x\text{-}\mu_{H20})$ / μ_{H20} , typically -1000 \leq HU \leq 3500

- We will use loosely the word "organ" to indicate a group of voxels (or even more than one group) made of the same "tissue" material (same HU value or in a given HU interval)
- The code handles each organ as a CG region, possibly in addition to other conventional "non-voxel" regions defined by the user
- The voxel structure can be complemented by parts written in the standard Combinatorial geometry
- The code assumes that the voxel structure is contained in a parallelepiped. This RPP is automatically generated from the voxel information.
- To describe a voxel geometry, the user provides the CT scan or equivalent data in a format understood by FLUKA by means of an external conversion program

Alghero, June 2011

The FLUKA voxel geometry

Preparation:

- Assign an organ index to each voxel. In many practical cases, the user will have a continuum of CT values (HU), and may have to group these values in intervals
- Each organ is identified by a unique integer ≤32767. The organ numbering does not need to be contiguous (i.e. "holes" in the numbering sequence are allowed.)
- One of the organs must have number 0 and plays the role of the medium surrounding the voxels (usually vacuum or air).

Practical issues for Medical Applications

General problems for MC calculations on CT scans

- How to assign realistic human tissue parameters (= materials) for MC Calculation ?
- How to find a good compromise between the number of different HU values (~ 3000-5000) and the materials to be considered in the MC ? (issues on memory and computation speed when attempting to treat each HU number as a different material !!!)
- How to preserve continuous, HU-dependent information when segmenting the HU numbers into intervals sharing the same "tissue" material ? (critical for ion range calculation in charged hadron therapy !!!)

Alghero, June 2011

G. Battistoni
CT stoichiometric calibration (I)													
CT segmentation into 27 materials of defined elemental composition (from analysis of 71 human CT scans)													
		$w_l(pp)$											
	H	н	С	N	0	Na	Mg	P	S	C1	Ar	ĸ	Ca
Ain Lung	-1000950			75.5	23.2						1.3		
	-950120	10.3	10.5	3.1	74.9	0.2		0.2	0.3	0.3		0.2	
Adinosa tissua	-120 - 83	11.6	68.1	0.2	19.8	0.1			0.1	0.1			
nuipose issue c	-8253	11.3	56.7	0.9	30.8	0.1			0.1	0.1			
	-5223	11.0	45.8	1.5	41.1	0.1		0.1	0.2	0.2			
	-22-7	10.8	35.6	2.2	50.9			0.1	0.2	0.2			
	8-18	10.6	28.4	2.6	57.8			0.1	0.2	0.2		0.1	
Soft tissue 3	19-80	10.3	13.4	3.0	72.3	0.2		0.2	0.2	0.2		0.2	
	80-120	9.4	20.7	6.2	62.2	0.6			0.6	0.3			
	120-200	9.5	45.5	2.5	35.5	0.1		2.1	0.1	0.1		0.1	4.5
	200-300	8.9	42.3	2.7	36.3	0.1		3.0	0.1	0.1		0.1	6.4
	300-400	8.2	39.1	2.9	37.2	0.1		3.9	0.1	0.1		0.1	8.3
	400-500	7.6	36.1	3.0	38.0	0.1	0.1	4.7	0.2	0.1			10.1
	500-600	7.1	33.5	3.2	38.7	0.1	0.1	5.4	0.2				11.7
	600-700	6.6	31.0	3.3	39.4	0.1	0.1	6.1	0.2				13.2
	700-800	6.1	28.7	3.5	40.0	0.1	0.1	6.7	0.2				14.6
	800-900	5.6	26.5	3.6	40.5	0.1	0.2	7.3	0.3				15.9
Skeletal tissue	900-1000	5.2	24.6	3.7	41.1	0.1	0.2	7.8	0.3				17.0
Shelerul IISSue	1000-1100	4.9	22.7	3.8	41.6	0.1	0.2	8.3	0.3				18.1
	1100-1200	4.5	21.0	3.9	42.0	0.1	0.2	8.8	0.3				19.2
	1200-1300	4.2	19.4	4.0	42.5	0.1	0.2	9.2	0.3				20.1
	1300-1400	3.9	17.9	4.1	42.9	0.1	0.2	9.6	0.3				21.0
	1400-1500	3.6	16.5	4.2	43.2	0.1	0.2	10.0	0.3				21.9
	1500-1600	3.4	15.5	4.2	43.5	0.1	0.2	10.3	0.3				22.5

G. B**Schmeider et al PMB 45, 2000**

CT stoichiometric calibration (II)

Assign to each material a "nominal mean density", e.g. using the density at the center of each HU interval (Jiang et al, MP 2004)



But "real density" (and related physical quantities) Alghvanies continuously with Hultovalue !!!

Rasterscan Method @ GSI / HIT



Ion species

p, ¹²C
 (later also ³He, ¹⁶O)

Beam delivery ➤Scanning with active energy variation (like @ GSI)

Required parameters:
255 Energy steps
4 Foci
10 Intensities

Heidelberg Ion Beam therapy Center



Start of clinical operation: November 2009

Mixed Radiation Field in Carbon Ion Therapy

¹²C (400 MeV/u) on water



Exp. Data (points) from Haettner et al, Rad. Prot. Dos. 2006 Simulation: A. Mairani PhD Thesis, 2007, PMB *to be published*

Mixed Radiation Field in Carbon Ion Therapy

¹²C (400 MeV/u) on water



Simulation: A. Mairani PhD Thesis, 2007, PMB to be published

The role of MC in ion therapy

Treatment planning systems (TPS) use analytical models

MC are increasingly used computational tools to support:

Startup and Commissioning of new facilities: e.g., beamline modeling and generation of TPS input data (*↓ meas. time*)

Validation of TPS absorbed and biological dose calculations: in water-equivalent system and in patient anatomy (CT)

Dedicated applications: imaging of secondary emerging radiation for treatment verification, like PET monitoring of ion therapy

Passively formed proton treatments @ MGH

FLUKA coupled with phase space information from a separate Geant4 MCcalculation (*Paganetti et al, MP 31, 2004*) modeling nozzle and modifiers







... Taking into account desired 4-10 mm focus @ ISO for higher E and physical limitation from scattering in monitor system and air

Generation of basic input data for TPS – depth dose profiles FLUKA calculation of depth-dose profiles in water w/wo ripple filter (RiFi)

for all the 255 energies delivered by accelerator for p and ¹²C



Generation of basic input data for TPS – Fragment Spectra

FLUKA calculation of fragment spectra in water w/wo ripple filter (RiFi) for 12 C (80 – 440 MeV/u)



Generation of basic input data for TPS – Fragment Spectra

FLUKA calculation of fragment spectra in water w/wo ripple filter (RiFi) for 12 C (80 – 440 MeV/u)



Forward recalculation of TPS treatment plans in water

(i.e. medium where plans are experimentally verified) FLUKA coupled with control file of raster scanning system + modeling of the beam-line

(F. Sommerer et al, EWG-MCTP Workshop, Ghent 2006, A. Mairani et al to be submitted)



Mairani, Parodi et al to be published

Forward recalculation of TPS treatment plans in water



Primary Beam H He Li Be B C







Forward recalculation of TPS treatment plans in water

(i.e. medium where plans are experimentally verified) FLUKA coupled with control file of raster scanning system + modeling of the beam-line



Mairani, Parodi et al to be published

MC versus TPS for proton therapy @ MGH Clivus Chordoma Patient



MC versus TPS for carbon ion therapy @ GSI Clivus Chordoma Patient – Absorbed Dose



Absorbed Dose Spread-Out Bragg Peak in the patient

A. Mairani PhD thesis 2007, PaviaA. Mairani *et al* IEEE 2008



Biological MC calculations: FLUKA coupled with external bio database



dose and cell survival



Biological MC calculations: FLUKA coupled with the Local Effect Model

Starting from the intrinsic LEM coefficients, the α_D and β_D parameters are obtained in terms of macroscopic dose applying the "*rapid approach*" described in :

PMB 51 (2006) 1959 M. Krämer and M. Scholz

The coupling of the LEM with FLUKA has been carried out using the Theory of Dual Radiation Action (TDRA) (A. M. Kellerer and H. H. Rossi, Radiat. Res. 75 (1978) 471):

*a biological system exposed to more than one radiation type will show synergism, implying that the total number of lesions is larger than the sum of the lesions produced by each single beam component, due to interactions between sub-lesions produced by different components.

A. Mairani et al, IEEE 2008 and PMB 2010

Biological MC calculations: comparison with experimental data and analytical calculations



Exp. data (points) courtesy of M. Scholz (GSI) Radiat. Environ. Biophys. 36 (1997) 59

Biological MC calculations:

comparison with experimental data and analytical calculations

Clinical calculation:

- Two opposing dose ramps with tissue sparing (as brain-stem)
- TRiP98 Analytical calculations: biological planning and optimization for CHO cells
- ✓ FLUKA-LEM: forward calculation of the optimized plan



Exp. Data and analytical calculations: Krämer et al, PMB 48 (2003) 2063 MC Calculations: A. Mairani et al, PMB 2010 submitted

Biological MC calculations:

comparison with experimental data and analytical calculations

Clinical calculation:

- ✓ Two opposing dose ramps with tissue sparing (as brain-stem)
- TRiP98 Analytical calculations: biological planning and optimization for CHO cells
- ✓ FLUKA-LEM: forward calculation of the optimized plan



Exp. Data and analytical calculations: Krämer et al, PMB 48 (2003) 2063 MC Calculations: A. Mairani et al, PMB 2010 submitted



A. Mairani et al, to be published

The principle of PET verification



By-product of irradiation (¹⁵O, ¹¹C, ¹³N...with $T_{1/2} \sim 2$, 20 and 10 min)

The principle of PET verification

*A(***r**) ≠ *D(***r**) Measured activity compared with calculation 1.2 1.2 — Activity Dose — Activity Dose ¹²C ions, E=212 A MeVProtons, E=110 MeV 1.0 1.0 Arbitrary units Arbitrary units 0.8 ¹¹C, 0.8 ¹⁵O, ¹¹C, ¹⁰C 0.6 0.6 0.4 0.4 0.2 0.2 ¹⁵O, ¹¹C *********** 0.0 0.0 20 60 100 40 80 -20 40 80 20 60 100 0 -20 0 K. Parodi et al, IEEE TNS 2005 Penetration depth / mm Penetration depth / mm

By-product of irradiation (¹⁵O, ¹¹C, ¹³N...with $T_{1/2} \sim 2$, 20 and 10 min)

Calculation model of β**+-activation**

FLUKA Monte Carlo code using

- Field-specific beam source information from Geant4 modeling of the nozzle and beam modifiers (*Paganetti et al, MP 31, 2004*)
- Planning CT (segmented into 27 material) and same CT-range calibration curve as TPS (Parodi et al MP 34, 2007, PMB 52, 2007)
- \succ Experimental cross-sections for β^+ -emitter production
- Semi-empirical biological modeling (Parodi et al IJROBP 2007)
- ➤ Convolution with 3D Gaussian kernel (7-7.5 mm FWHM)



In-beam PET: ion beam fragmentation

- Final goal: simulation of β⁺ emitters generated during the irradiation
- In-beam treatment plan verification with PET
- Work in progress: FLUKA validation
 - Comparison with experimental data on fragment production (Schall et al.)
 - ¹²C, ¹⁴N, ¹⁶O beams, 675 MeV/A
 - Adjustable water column 0-25.5 cm
 - Z spectra of escaping fragments for Z>4
 - Cumulative yield of light fragments
 - Simulation: corrections applied for angular acceptance and for material in the beam upstream the water target
 - Comparison with experimental data on β^+ -emitter production (Fiedler et. al.)

Alghero, June 2011

G. Battistoni

β⁺-Activity after Irradiation







Measured 10 - 20 min after irradiation, therefore dominated by ^{11}C

- Further work: processing with same software than experiment more primaries for better statistic

Final results are expected for the end of this year G. Battistoni

Backprojections: FLUKA vs Exp data



Applications of FLUKA to p therapy @ MGH

Input phase-space provided by H. Paganetti, MGH Boston



Prescribed dose: 1 GyE MC : ~ 5.5 10⁶ protons in 10 independent runs (11h each on Linux Cluster mostly using 2.2GHz Athlon processors)

Alghero, June 2011

G. Battistoni

Applications of FLUKA to p therapy @ MGH

400

200

-200

-400

-600

0

mGy

Parodi et PMB 52, 2007







mGy

mGy

800

600

400

200

-200

-400

-600

-800

0







K. Parodi et al, IJROBP 2007

Applications of FLUKA to p therapy @ MGH



Prescribed dose: 2 GyE MC : ~ 7.4 10⁷p in 12 independent runs (~ 130h each on 2.2 GHz Linux cluster)

Alghero, June 2011

G. Battistoni





)07 ... and FLUKA-voxel functionali used at HIT ...

Alghero, June 2011

G. Battistoni

β^+ emitters for ion beams: phantom experiments

Application of FLUKA to PET monitoring of ion species (e.g. ¹²C, ¹⁶O) based on *internal nuclear models*

Simulation of *imaging process* (β^+ -decay, propagation of e^+ and annihilation photons, detection) same as for measured data

- Exact replica of the experimental setup, PET heads included
- FLUKA irradiation+decay features exploited
- MC y's reaching PET heads converted to list-mode data by modified PETSIM¹
- Backprojection with same routines as in experiment



Alghero, June 2011 F. Sommerer PhD Thesis, 2007, F. Sommerer et al PMB 54 2009
