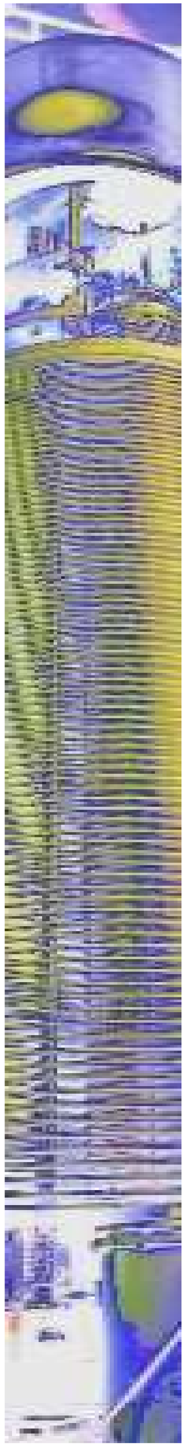
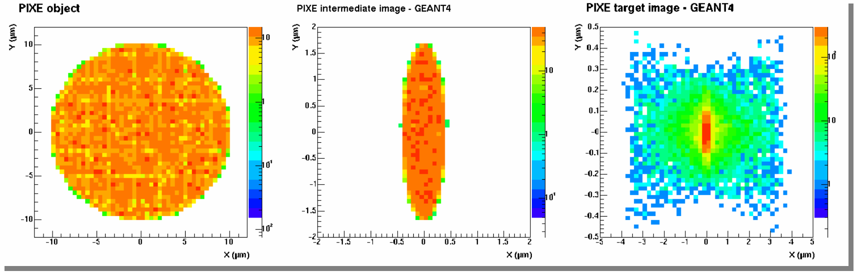


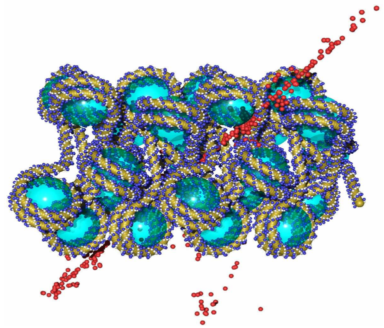
Geant4 simulations for microdosimetry at the cellular level and nanobeam design

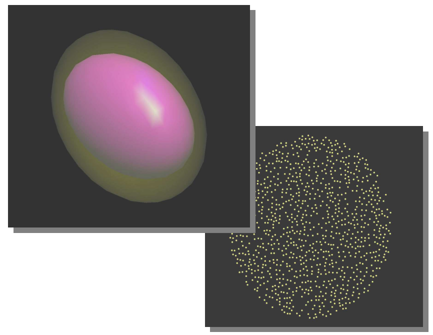
Sébastien Incerti

on behalf of the Physics Biology group



Centre d'Etudes Nucléaires de Bordeaux - Gradignan
IN2P3/CNRS
Université Bordeaux 1
33175 Gradignan
France





Geant4 2005
November 3rd-10th, 2005

CENBG

CNRS CENTRE NATIONAL DE LA RECHERCHE SCIENTIFIQUE

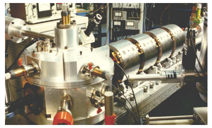
IN2P3 Institut National de Physique Nucléaire et de Physique des Particules

Université Bordeaux 1 Sciences Technologies

The CENBG Physics Biology group in October 2005

Consequences of environmental stress at the biological tissue and cell scales

Philippe MORETTO
Professor
Bordeaux 1 University



Two facilities @ CENBG on a state-of-the-art low energy Singletron electrostatic accelerator (p, d, α up to 3.5 MeV)

- a microbeam line (resolution in vacuum < 1 µm) for
  - bio-sample analysis through Scanning Transmission Ion Microscopy, Particle Induced X-ray Emission & Rutherford Back Scattering
  - targeted cellular irradiation in single ion mode
- an upcoming nanobeam line (~2006) mainly for analysis with a resolution in vacuum of about 50 nm

3D microtomography

Claire HABCHI
Teaching Assistant
Bordeaux 1 University

Duy Thuy NGUYEN
Graduate student
Ministère des Affaires Etrangères
(France)

Low dose irradiation & cellular response

Hervé SEZNEC
Research Associate
CNRS/IN2P3/SDV

Thomas POUTHIER
Graduate student
BDI CNRS/COGEMA

Simulations (microdosimetry & ray tracing)

Sébastien INCERTI
Research Associate
CNRS/IN2P3

Qianmei ZHANG
Post-doc fellow
Bordeaux 1 University

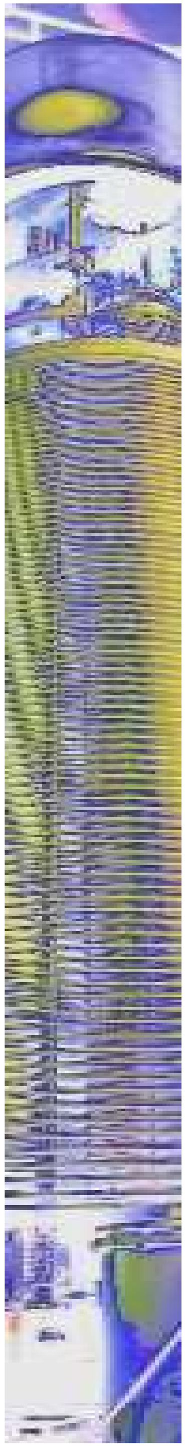
Why Monte Carlo simulation ?

Looking for a simulation tool able to perform…

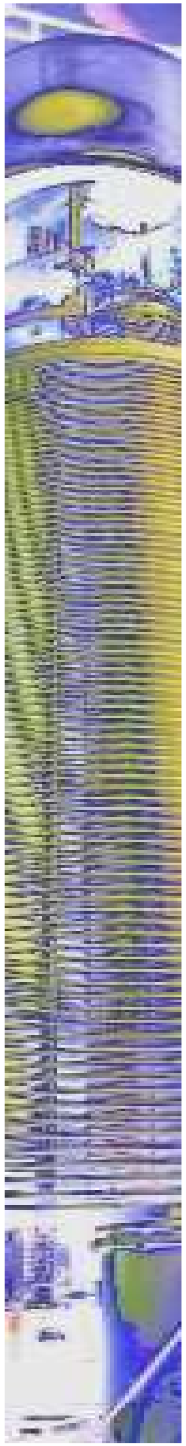
- **True ray-tracing**
  - **ion transport** in focusing quadrupoles to characterize the **microbeam line** performances and predict / adjust the **nanobeam line** focusing capabilities
  - understand and reduce **scattering along the line** :
    collimator edges, diaphragms, pipe residual air…
  - understand and reduce **scattering inside the cellular irradiation chamber** :
    ion detector, extraction window, culture foil where cells attach…

- **Microdosimetry and cell damage**
  - estimate the **absorbed dose** in single ion irradiation mode
  - model **DNA damage** and survival at the cell level
  - compare with **other irradiation techniques** (alpha emitters, macro beam)

Geant4

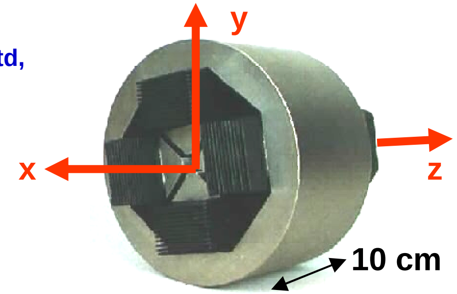


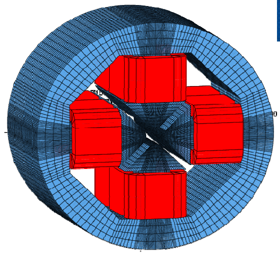
Ray-tracing at the sub-micron scale



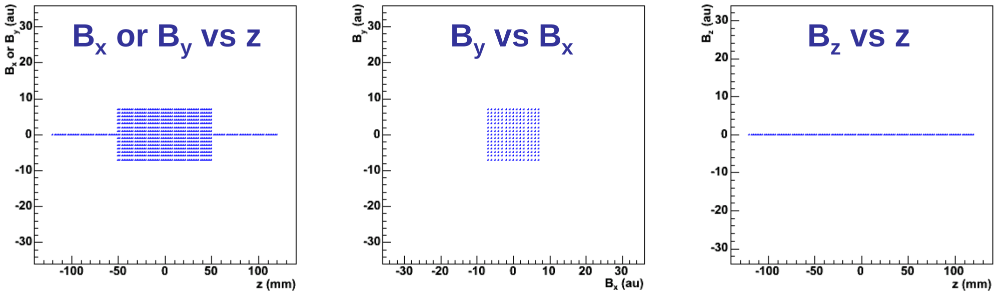
Field models for the nanobeam line quadrupole magnets

Oxford Microbeams Ltd, U.K.

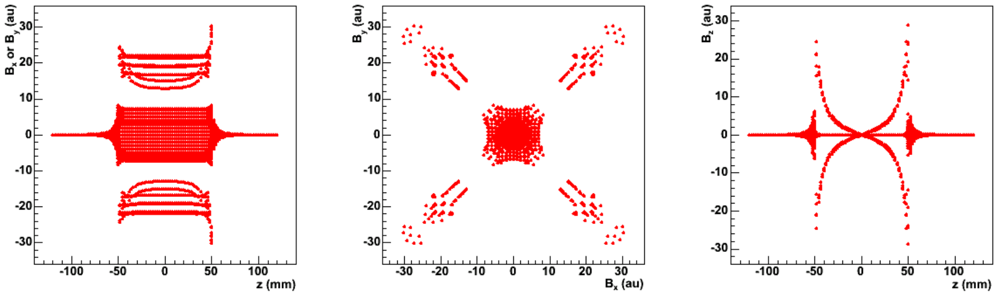




- Map recently computed with VF Opera 3D
- mesh :
  - 14 x 14 x 240 mm^3
  - 27225 nodes



Simple quadrupole field model like in class G4QuadrupoleMagField $B_x = y\,G$ and $B_y = x\,G$

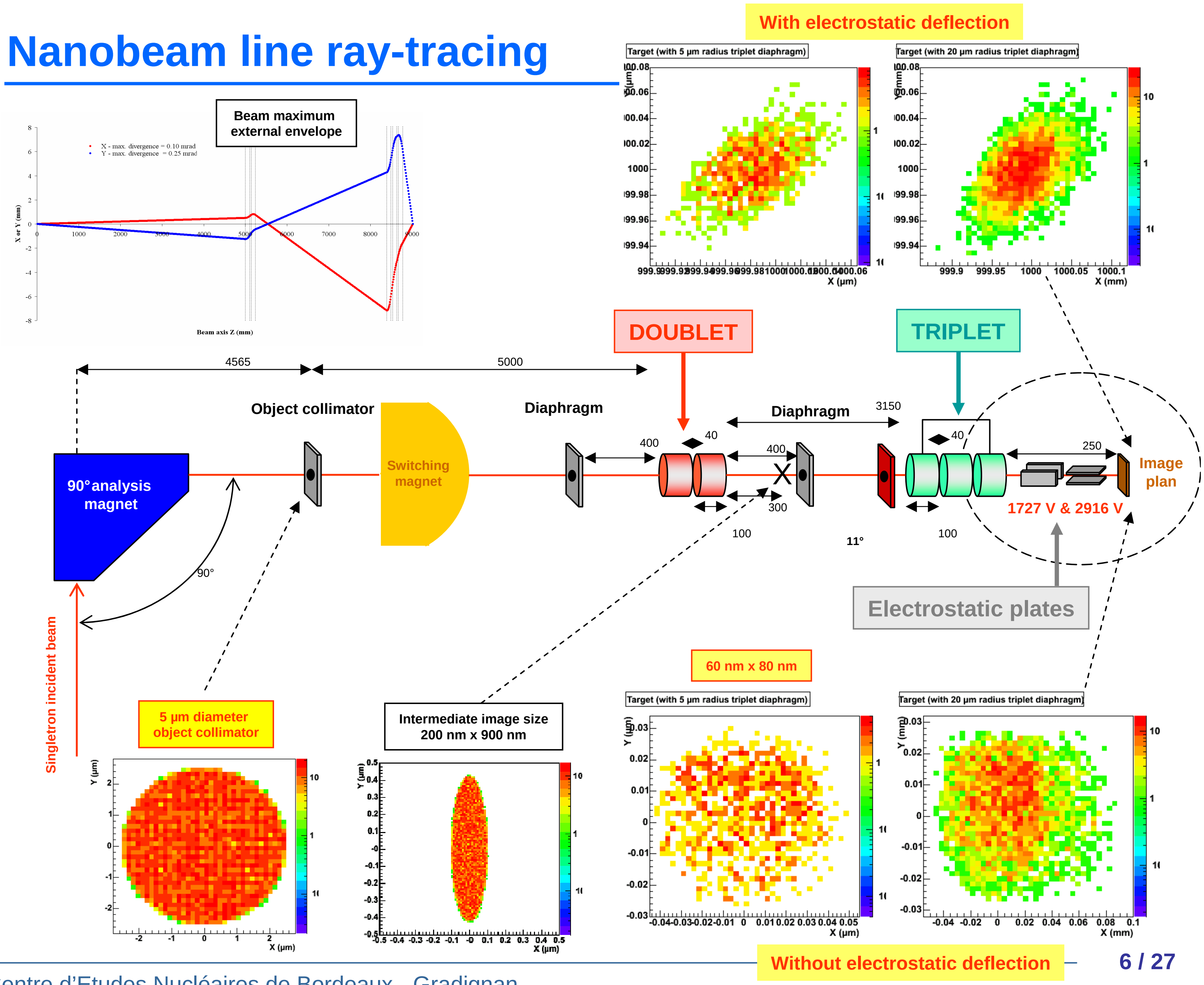


3D quadrupole field map from Opera 3D & 3D linear interpolation from advanced Purging Magnet code

Gradients for 3.5 MeV protons	G_1 (T/m)	G_2 (T/m)	G_3 (T/m)	G_4 (T/m)
Simple field model	-11.97863	16.50520	9.866786	-6.244526
3D map field	-12.1492	16.7577	9.8990726	-6.2398758

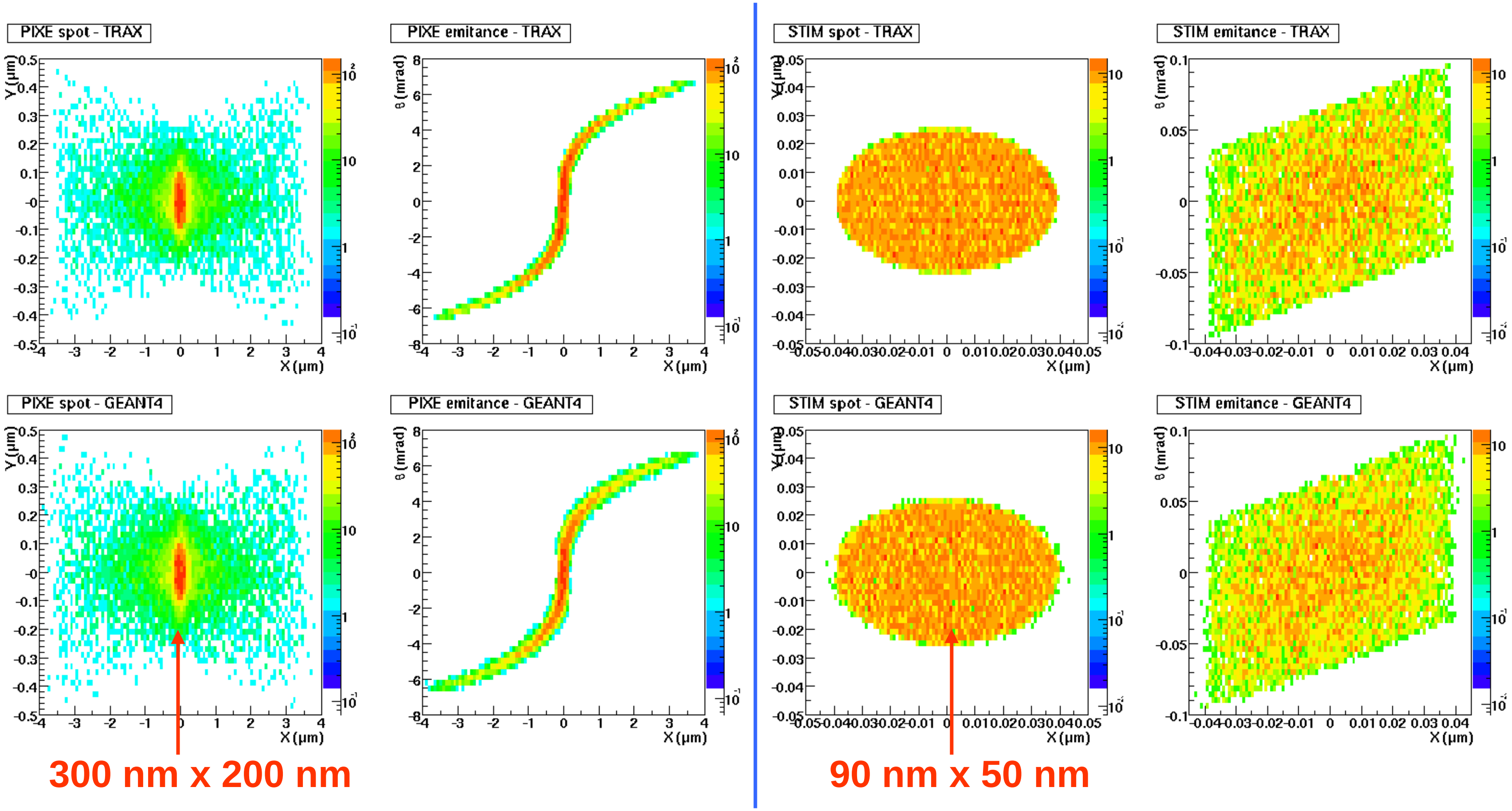
Gradient computation fully automated with Geant4

Nanobeam line ray-tracing



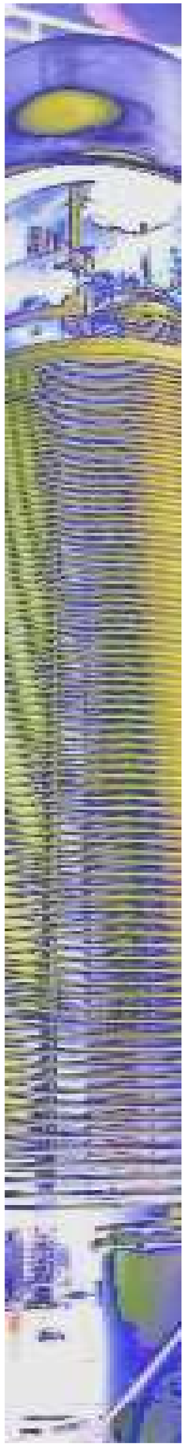
Comparison in high (PIXE) and low flux (STIM) modes

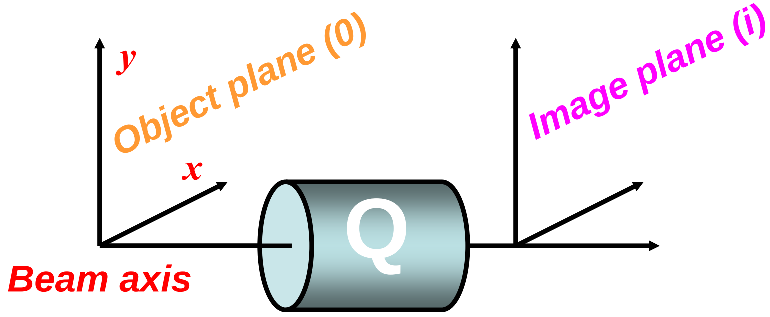
Geant4 versus TRAX (reference)



- Nice agreement between **TRAX** and **Geant4** (square field model, no map)
- Sharp STIM image, distorted PIXE image (chromatic and spherical aberrations)
- Compatible with probe size requirements
- Pure vacuum, no collimators

Beam optics





$$x = \cos\Phi \sin\theta$$
$$y = \sin\Phi$$
$$z = \cos\Phi \cos\theta$$

$$x_i = f(x_0, y_0, \theta_0, \Phi_0, \delta, Parasitic)$$

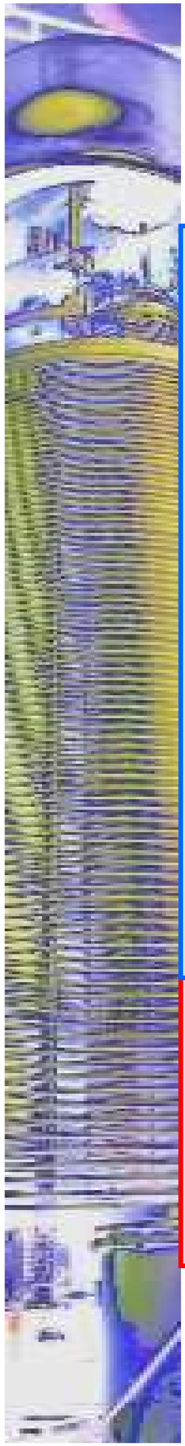
$$y_i = g(x_0, y_0, \theta_0, \Phi_0, \delta, Parasitic)$$

$$x_i = A_0 + A_1 x_0 + A_2 y_0 + A_3 \theta_0 + \ldots + A_n \nu_1^j \nu_2^k \nu_3^l + \ldots$$

A_n : aberration coefficient of order $j + k + l$ written $A_n = \left\langle x \middle| \nu_1^j \nu_2^k \nu_3^l \right\rangle$

Example : $< x \,|\, \theta\Phi^2 >$

$\delta = \Delta P / P = \Delta E / 2E$



List of quadrupole dominant aberration coefficients

Order and Type	Coefficients	Remarks
1st INTRINSIC	$< x \mid x > = 1/D_x$	Horizontal demagnification
	$< y \mid y > = 1/D_y$	Vertical demagnification
	$< x \mid \theta >$	Horizontal astigmatism (zero for correctly focused image)
	$< y \mid \Phi >$	Vertical astigmatism (zero for correctly focused image)
1st PARASITIC	$< x \mid U_n >$	Horizontal translation of quadrupole n
	$< y \mid V_n >$	Vertical translation of quadrupole n
	$< x \mid \alpha_n >$	Tilt in xz plane of quadrupole n
	$< y \mid \beta_n >$	Tilt in yz plane of quadrupole n
2nd INTRINSIC	$< x \mid \theta\delta >$	Chromatic aberration ($\delta = \Delta P/P$)
	$< y \mid \Phi\delta >$	Chromatic aberration
	$< x \mid x\delta >$	little effect (small object size)
	$< y \mid y\delta >$	little effect (small object size)
2nd PARASITIC	$< x \mid \Phi\rho_n >$	Rotation of quadrupole n about optical axis (x and y planes coupled)
	$< y \mid \theta\rho_n >$	Rotation of quadrupole n about optical axis (x and y planes coupled)
	$< x \mid \theta\varepsilon_n >$	Excitation changes (power supply ripple, ε is % change in excitation)
	$< y \mid \Phi\varepsilon_n >$	Excitation changes (power supply ripple, ε is % change in excitation)
3rd INTRINSIC	$< x \mid \theta^3 >$	Spherical or aperture aberration
	$< y \mid \Phi^3 >$	Spherical or aperture aberration
	$< x \mid \theta\Phi^2 >$	Spherical or aperture aberration
	$< y \mid \Phi\theta^2 >$	Spherical or aperture aberration
5th INTRINSIC	$< x \mid \theta^5 >$	Negligible in current systems
	$< y \mid \Phi^5 >$	Only after spherical aberration has been corrected **using octupoles**

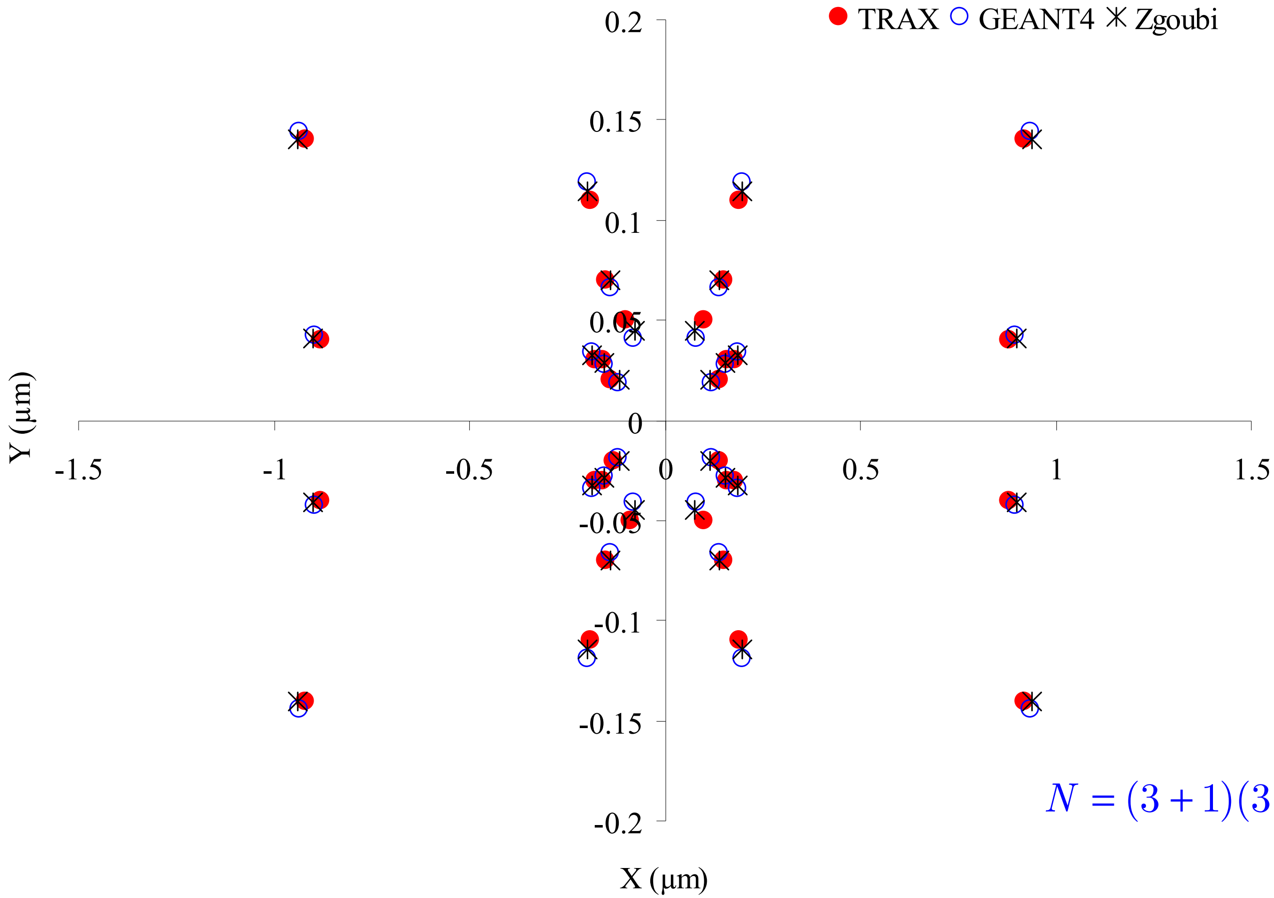
MATRIX + RAY TRACING

RAY TRACING

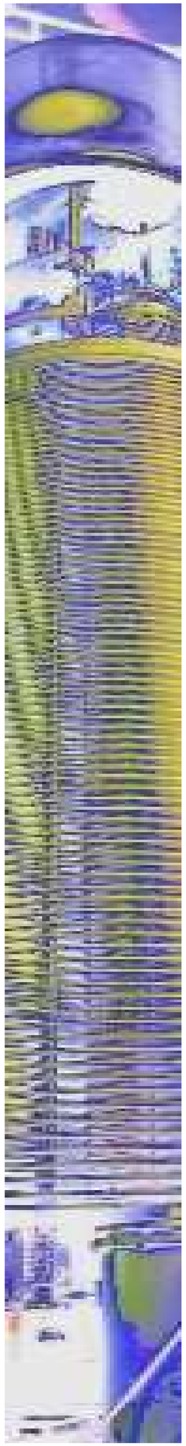
G. W. Grime and F. Watt, Beam Optics of Quadrupole Probe-Forming Systems, Adam Hilger Ltd., Bristol (1983)

Geant4 ray tracing capabilities

- Calculation up to any order for **TRAX** (ray-tracing reference code in the microbeam community) and **Geant4**, up to order three with **Zgoubi (second reference code)**
- $N = 32$ rays generated from a point source to reach order 3 in θ, Φ and order 1 in δ
- 32 coefficients A_n extracted from matrix inversion of the 32 ray positions on target



$$N = (3+1)(3+1)(1+1)$$



Quantitative predictions : intrinsic aberration coefficients

	Intrinsic aberration coefficients			
	TRAX	Geant4 3D MAP	Geant4 square (1)	Geant4 square (2)
$D_x = \langle x\|x \rangle$	6.3557E+01	6.36174+01	6.356E+01	6.3558E+01
$\langle x\|\theta \rangle$	-3.4937E-01	-1.04303E+02	5.3677E-01	-4.9865E-02
$\langle x\|\theta\delta \rangle$	-2.0354E+03	-2.05255E+03	-2.0331E+03	-2.0328E+03
$\langle x\|\theta\phi^2 \rangle$	3.5789E+02	-1.50558E+03	3.5625E+02	3.597E+02
$\langle x\|\theta^3 \rangle$	3.0893E+03	-5.4201E+04	3.0893E+03	3.0913E+03
$D_y = \langle y\|y \rangle$	9.9409E+01	9.87808E+01	9.9411E+01	9.9413E+01
$\langle y\|\phi \rangle$	-3.6262E-02	-1.59662E+01	1.2357E-01	8.9776E-02
$\langle y\|\phi\delta \rangle$	-3.6979E+02	-3.6385E+02	-3.7019E+02	-3.7018E+02
$\langle y\|\theta^2\phi \rangle$	2.2920E+02	1.39732E+04	2.2980E+02	2.2916E+02
$\langle y\|\phi^3 \rangle$	1.4896E+02	-8.81738E+02	1.4939E+02	1.4856E+02

3D map : spherical terms dominant

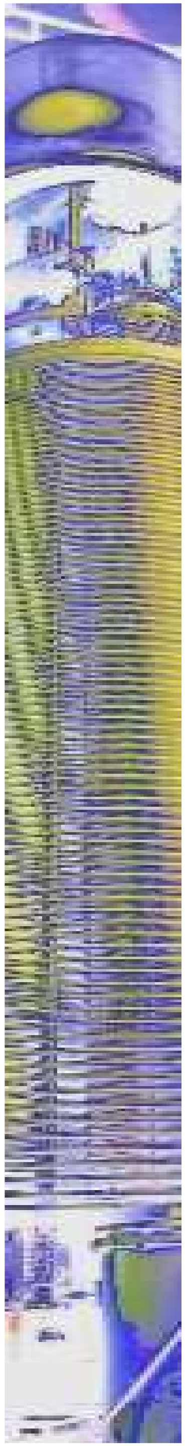
(1) using TRAX's gradients
(2) using GEANT4's gradients

units are µm, mrad and %

Next tasks

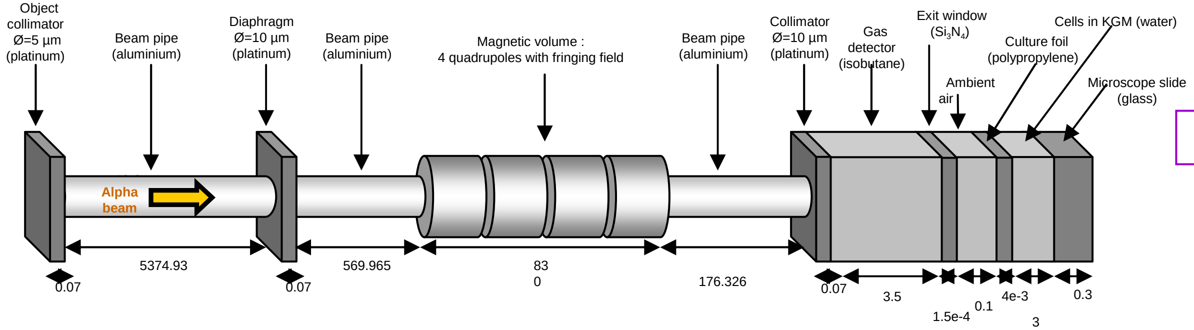
- increase **field map granularity** around paraxial region and investigate spherical terms dominance & parasitic
- compare with **Enge**'s fringing field model
- use nanobeam line simulation for **fine alignment** (grid-shadow techniques)
- investigate effect of **multiple scattering in very low pressure** residual air (Geant4 VS experiment)

Microdosimetry at the cellular scale

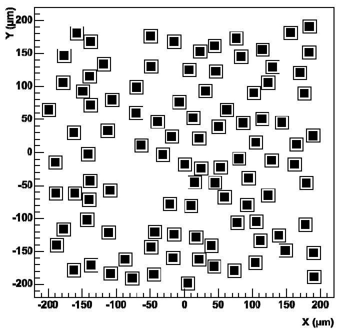


Cellular irradiation setups

CENBG Focused Microbeam

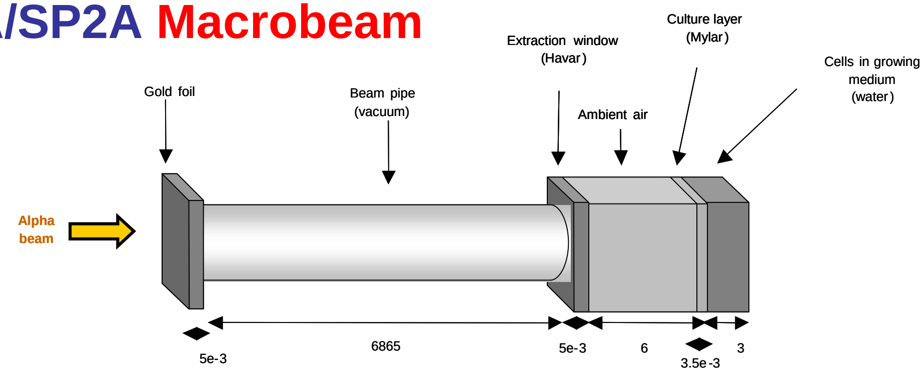


Cell layer in growing medium

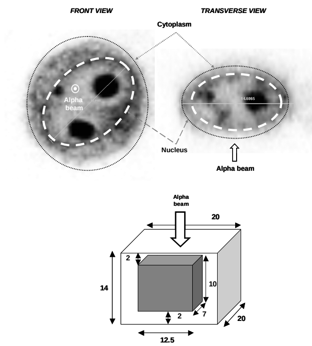


- 100 000 cells / 1.54 cm ²
- Nuclei distant of at least 20 µm from each other
- No overlap

CEA/SP2A Macrobeam

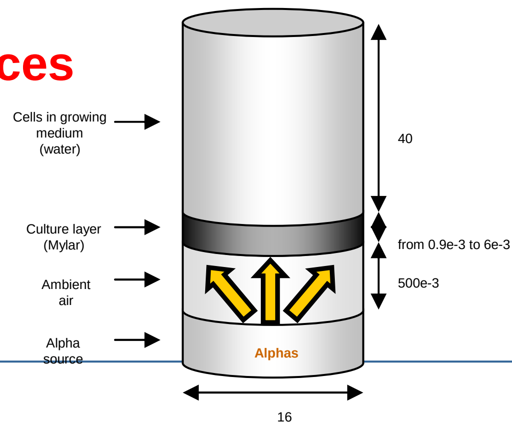


Two « reasonable » cell geometries



CEA/SP2A Electrodeposited sources

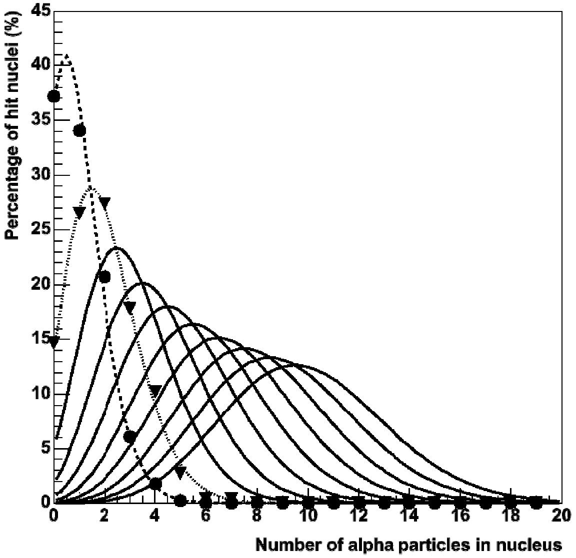
238/239 Pu



Hits and absorbed dose distributions

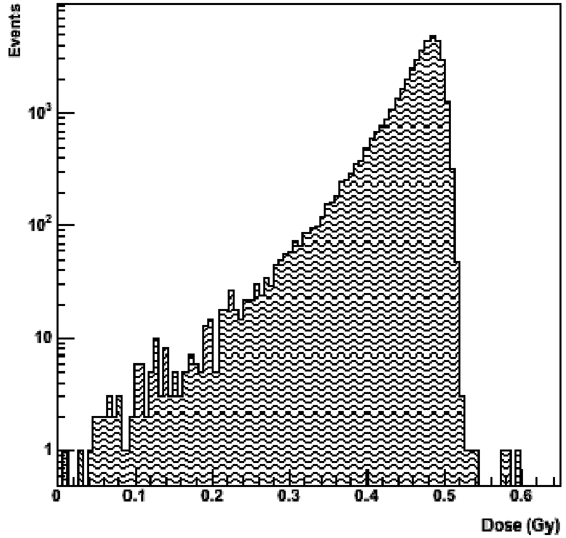
CENBG Microbeam

CEA Macrobeam



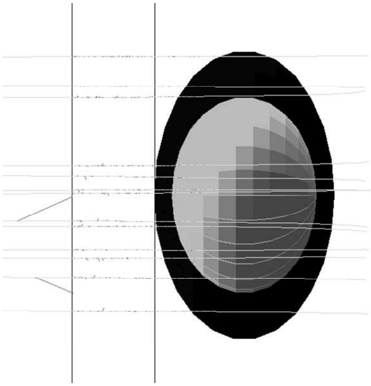
Percentage of hit nuclei

within the **parallelepiped cell** population irradiated with the CEA/DPTA **9.3 MeV** alpha macrobeam. The **plain circles** represent Geant4 predictions and the dashed curve shows the corresponding **Poisson fit**, with a **mean equal to one**. The plain triangles and the dotted curve correspond to a Poisson distribution of **mean 2**. For illustration, the other plain curves show Poisson fits for means ranging respectively **from 3 to 10**

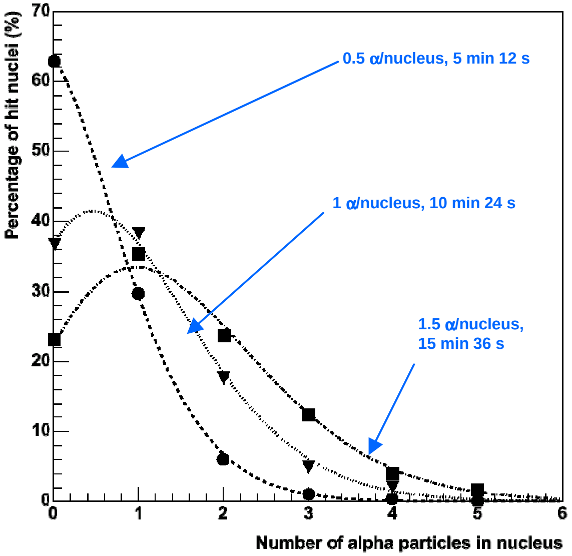


Absorbed dose distribution

within an **elliptic** nucleus for **3 MeV** incident alphas. The dose reaches **0.4 ± 0.1 Gy / alpha**. About **0.5 %** of incident alphas crossing the culture foil hit neighbor cells.



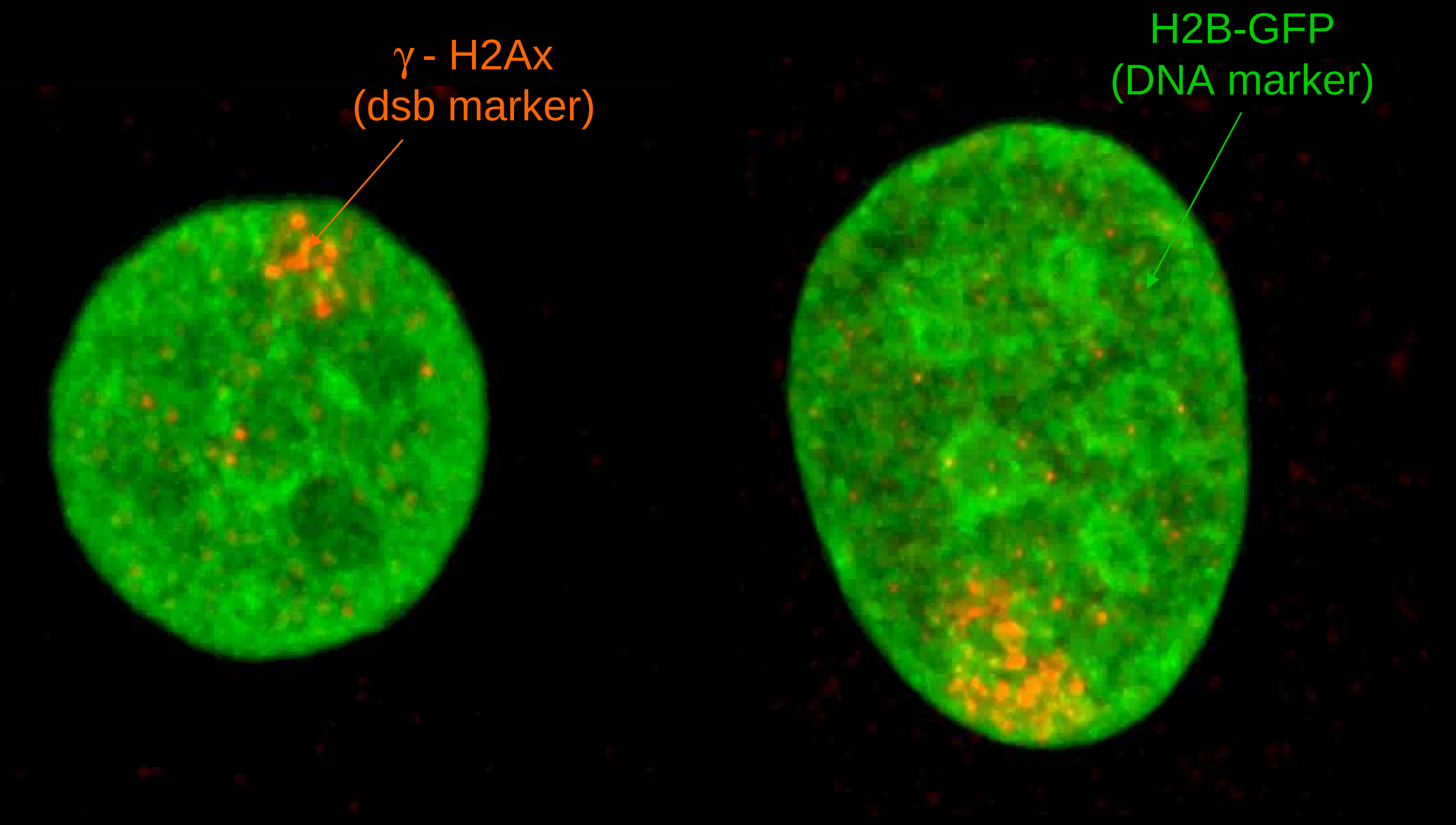
CEA Elec. Sources



Percentage of hit nuclei

within the **ellipsoid cell** population irradiated with the Pu alpha emitter through a mylar thickness of **0.9 µm** for an irradiation time of **5 min 12 s** (plain circles), **10 min 24 s** (plain triangles) and **15 min 36 s** (plain squares). The corresponding **Poisson fits** are shown. The mean for an irradiation time of 5 min 12 s (dashed line) reaches **0.5 alpha per nucleus** and is proportional to the irradiation duration (dot line for 10 min 24 s and mean of **1.0 alpha per nucleus** ; dot-dashed line for 15 min 36 s and mean of **1.5 alpha per nucleus**).

HaCat nucleus confocal imaging after irradiation



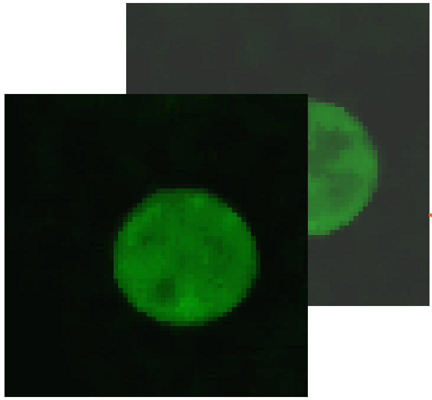
After irradiation with **5** alphas (3MeV)

After irradiation with **50** alphas (3 MeV)

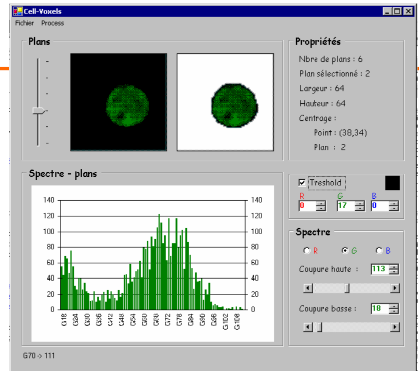
Dedicated keratinocyte cell line expressing the histone **H2B-GFP protein** and immunofluorescence using an antibobody against **phosphoryled H2AX histones (γ-H2AX)**

Realistic cellular geometries

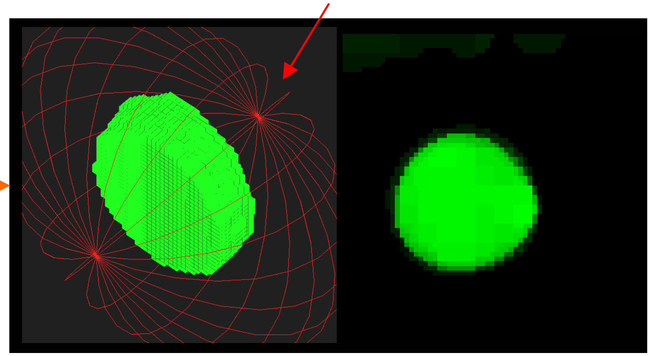
- Estimation of the **absorbed dose** : need for a realistic geometry
- Conversion of **confocal microscopy images** into Geant4 **parameterised volumes** (G4PVParameterisation) for the cell cytoplasm and the cell nucleus



Stack of 2D confocal images of nucleus marked with H2B-GFP (size 64x64)



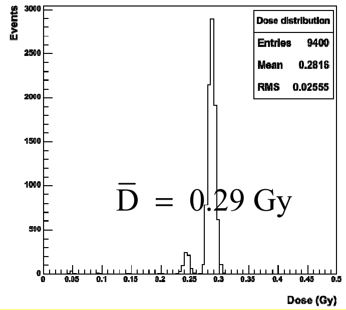
Ellipsoid cytoplasm (KamLAND)
(not marked yet)



Geant4 nucleus model
4015 voxels
(0.396 x 0.396 x 0.611 μm³ each)

3D reconstruction of confocal images

VC++ conversion application
- Pixel extraction
- RGB noise subtraction
- Centering
- Voxel local coordinates and intensity



3 MeV incident alphas (10^3)

Next tasks
- **Resolution** increase (256x256 and above) expected for **cytoplasm** and **nucleus**
- Average **nucleus chemical composition** will be measured from STIM, PIXE, RBS @ AIFIRA

Going beyond “à la PARTRAC”

Most advanced simulation tool of radiation damage at DNA level

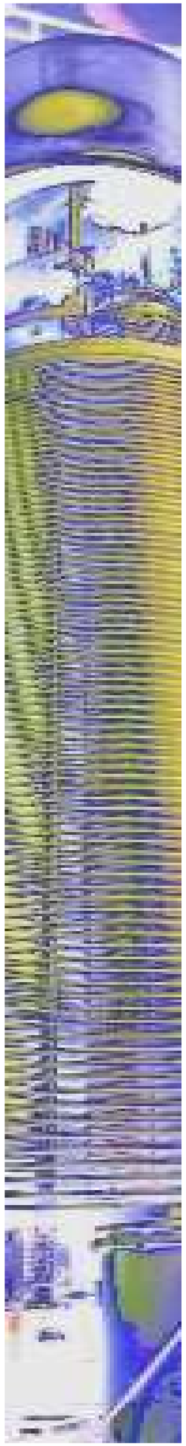
Modular structure written by W. Friedland *et al.* at GSF, Munich (20 years) :

- **simulation of cellular nucleus DNA content**
  Geometry module
- **simulation of proton or alpha interactions through the chosen cell geometry**
  Track structure module
- **simulation of secondary electron interactions**
  Track structure module

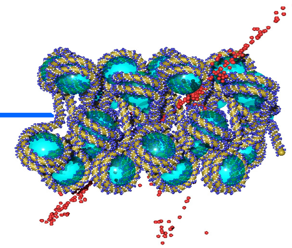
Geant4 DNA

- **simulation of damages to DNA (direct hits and OH. radicals)**
  Effect module
- **simulation of chemical effects of species (pre-chemical & chemical)**
  Chemistry module
- **extraction of biological damages (ssbs, dsbs, fragments,…)**
  Damage module

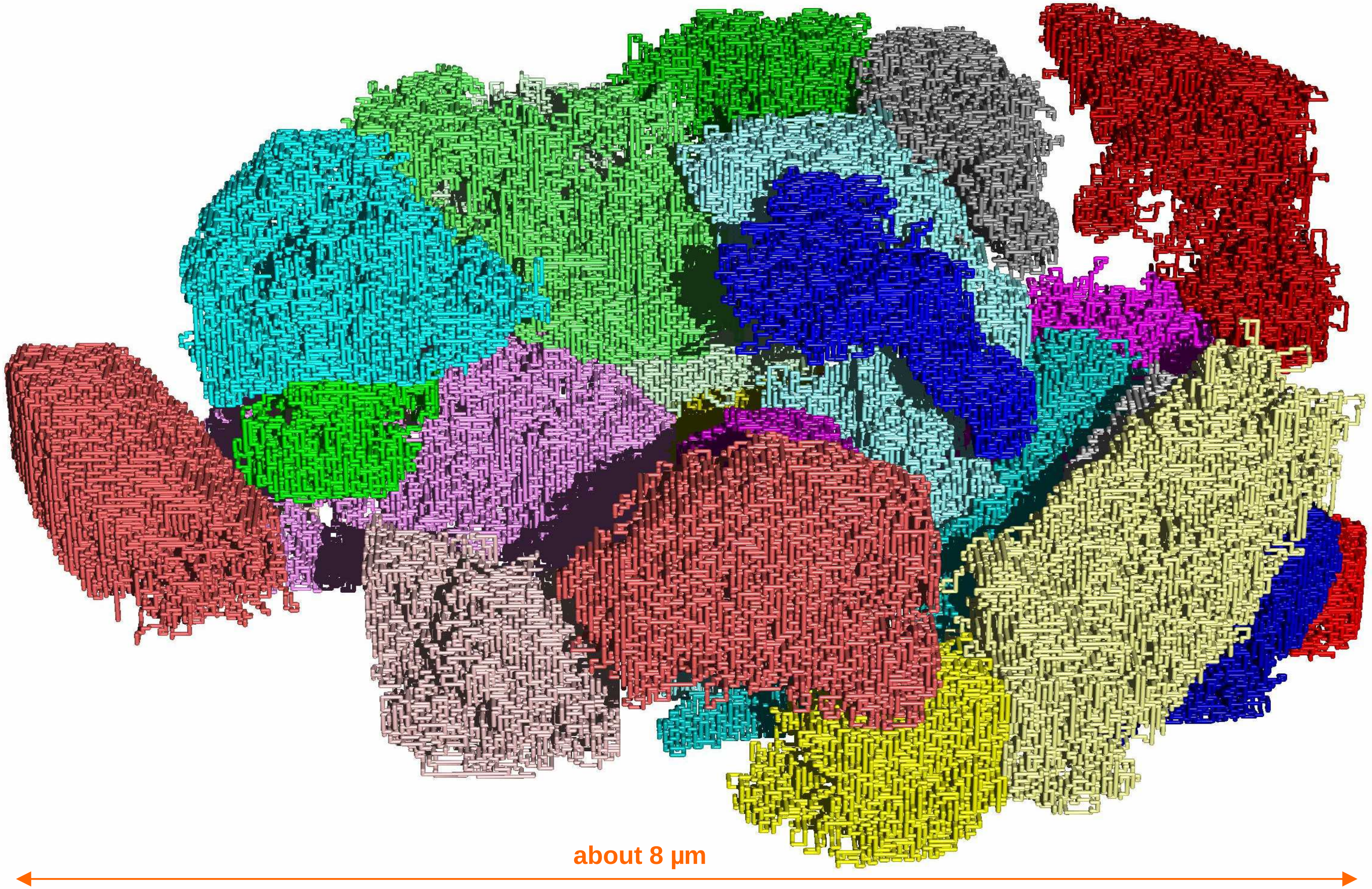
PARTRAC simulates processes
from the initial irradiation (t = 0) up to t = 10^{-6} s.
Repair processes are not simulated yet.



The nucleus geometry in PARTRAC



- human fibroblast cell nucleus
- 46 chromosomes
- 6 Gbp of chromatin
- irregular crossed linker structure
- atom by atom approach (center coordinates and Van der Waals radius)



R. Friedland *et al.*, RPC 72 (2005) 279-286

Geant4-DNA

Simulation of Interactions of Radiation with Biological Systems at the Cellular and DNA Level

Based on
Geant 4

Partly funded by

R. Capra, S. Chauvie, R. Cherubini, Z. Francis, S. Gerardi, S. Guatelli, G. Guerrieri, S. Incerti, B. Mascialino, G. Montarou, Ph. Moretto, P. Nieminen, M.G. Pia, M. Piergentili, C. Zacharatou

+ biology experts (E. Abbondandolo, G. Frosina, E. Giulotto *et al.*)

Geant4-DNA : programme

- Geant4-based "sister" activity to the Geant4 Low-Energy Electromagnetic Working Group
- Simulation of nano-scale effects of radiation at the cell and DNA level
- Three levels
  - Macroscopic : calculation of dose, develop useful associated tools
  - Cell : cell modelling, processes for cell survival, damage etc
  - DNA : DNA modelling, physics processes at the eV scale, processes for DNA strand breaking, repair…
- On-going activities : anthropomorphic phantoms, cell survival models, low energy physics extensions down to the eV scale, etc...
- Key elements
  - Rigorous software process
  - Collaboration with domain experts (biologists, physicians)
  - Team including groups with cellular irradiation facilities

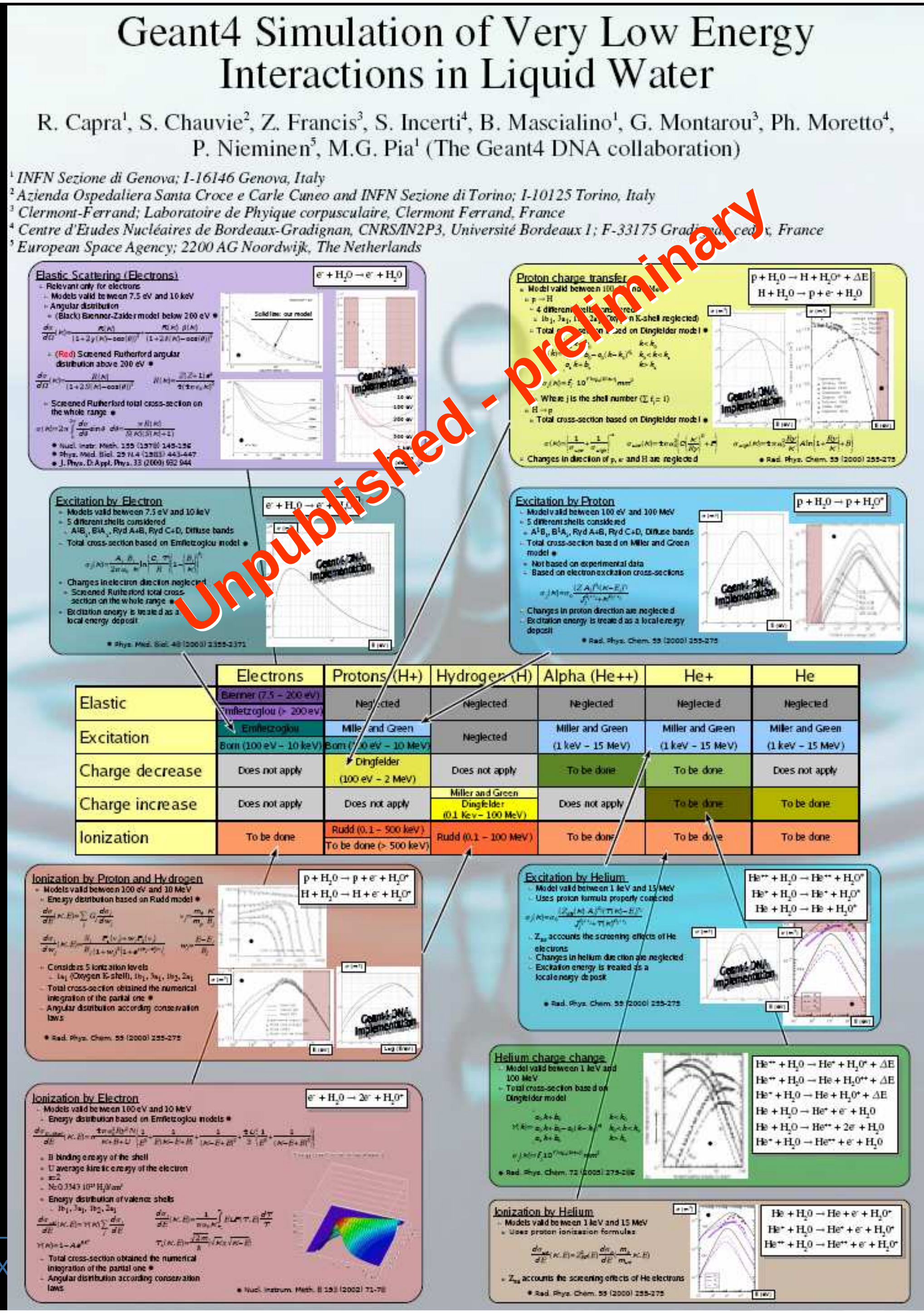
Geant4 DNA Physics processes
will be presented in a few days at the

14th Symposium on microdosimetry
Venezia, Italy, 13-18 November 2005

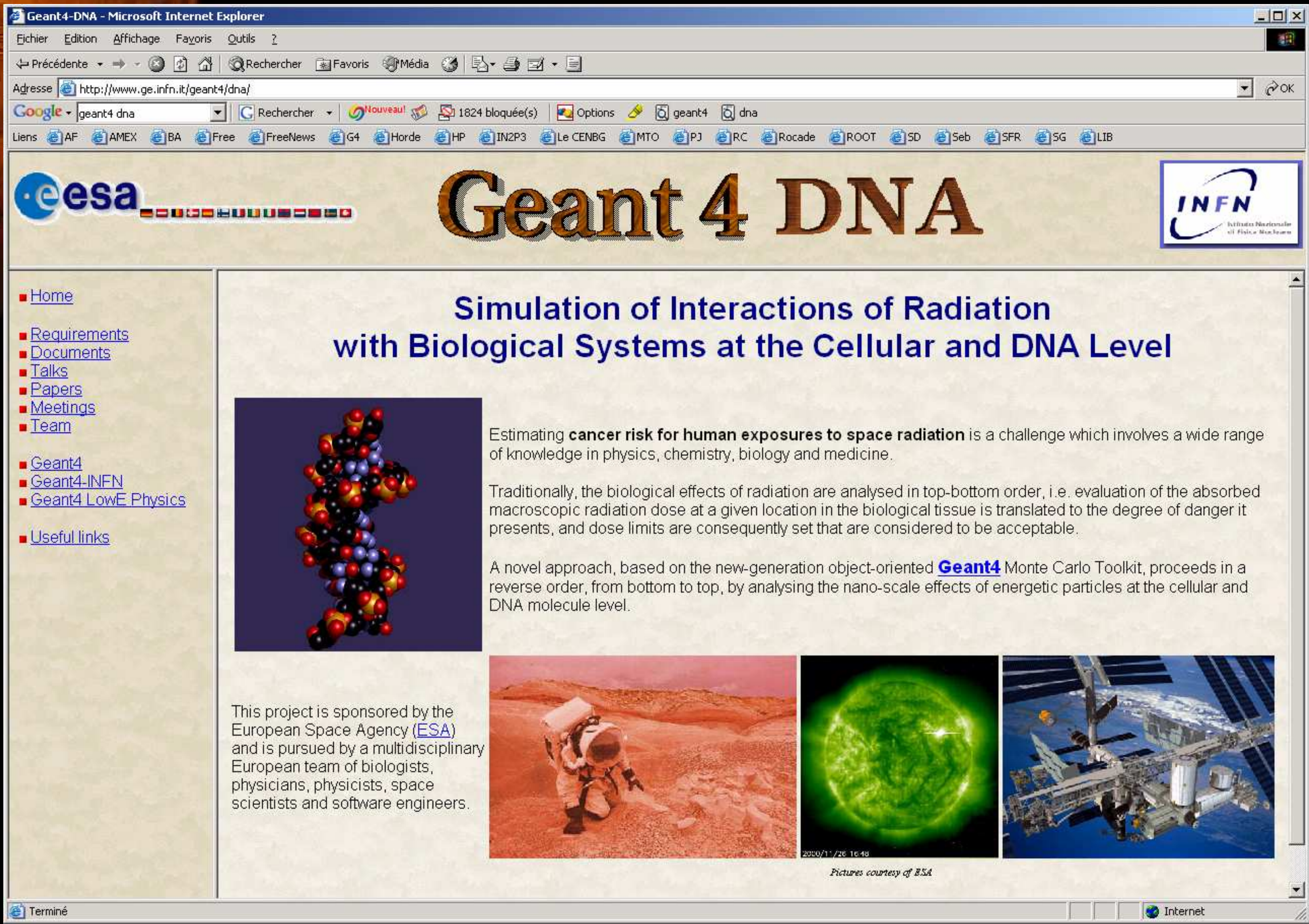
by the Geant4-DNA collaboration

and in a few minutes

see Ziad FRANCIS' talk



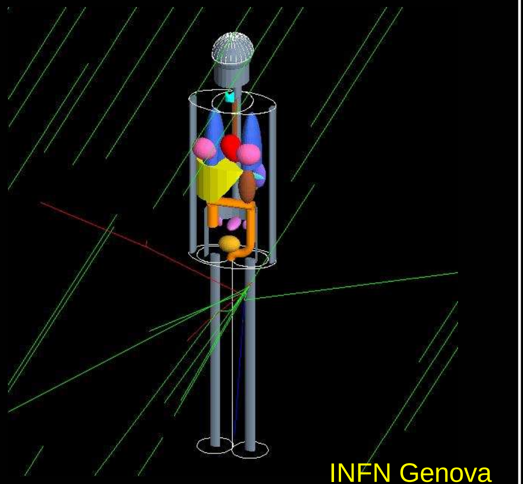
http://www.ge.infn.it/geant4/dna




esa
Aurora
European Programme for the
Exploration of the Solar System
The objective of the Aurora Programme is first to formulate and then to implement a European long-term plan for the robotic and human exploration of solar system bodies holding promise for traces of life.
MARE AUSTRALE
MARE ERYTHRAEUM

Scenario for AURORA

Geant4 simulation
space environment
+
spacecraft, shielding etc.
+
anthropomorphic phantom



Dose in
organs at risk

Phase space input
to nano-simulation

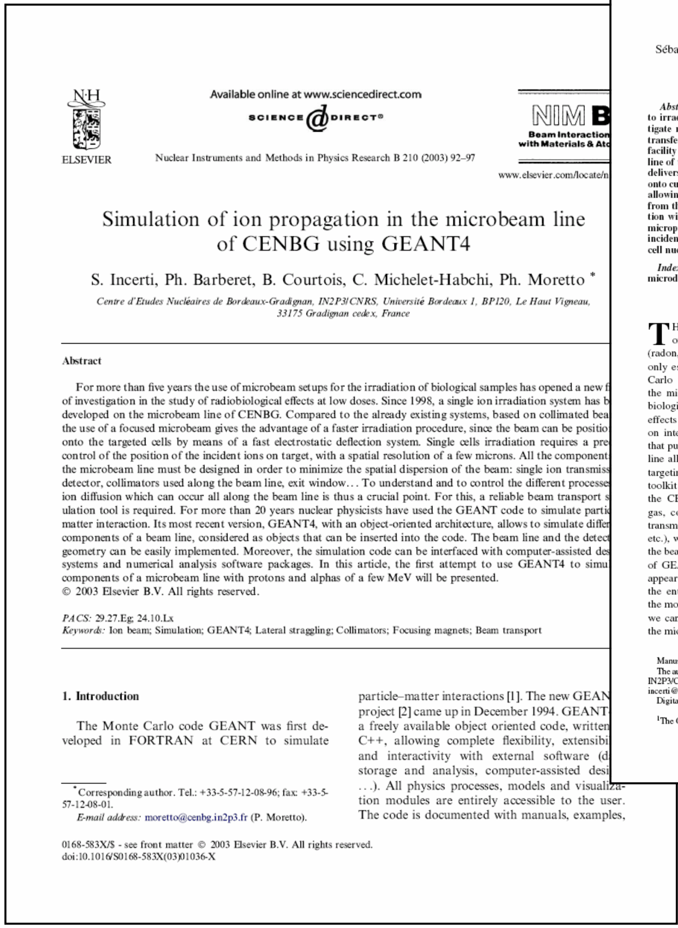
Geant4 simulation
with biological
processes at cellular
level (cell survival,
cell damage…)

Oncological risk to
astronauts

Risk of nervous
system damage

Geant4 simulation with
physics at eV scale
+
DNA processes

Validations of Geant4 for focused micro & nanobeams

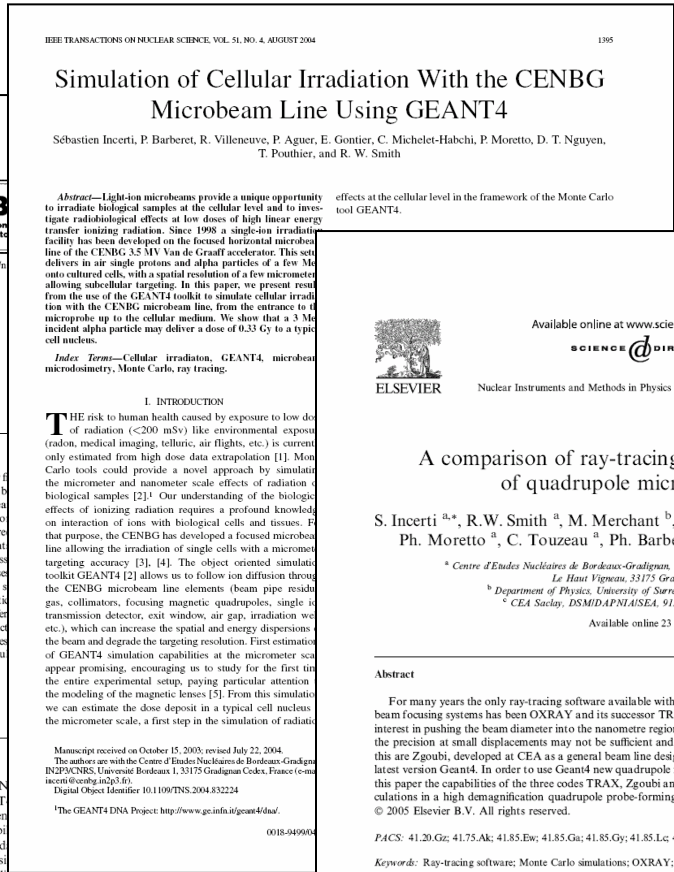


Nuclear Instruments and Methods in Physics Research B 210 (2003) 92–97

Simulation of ion propagation in the microbeam line of CENBG using GEANT4

S. Incerti, Ph. Barberet, B. Courtois, C. Michelet-Habchi, Ph. Moretto *

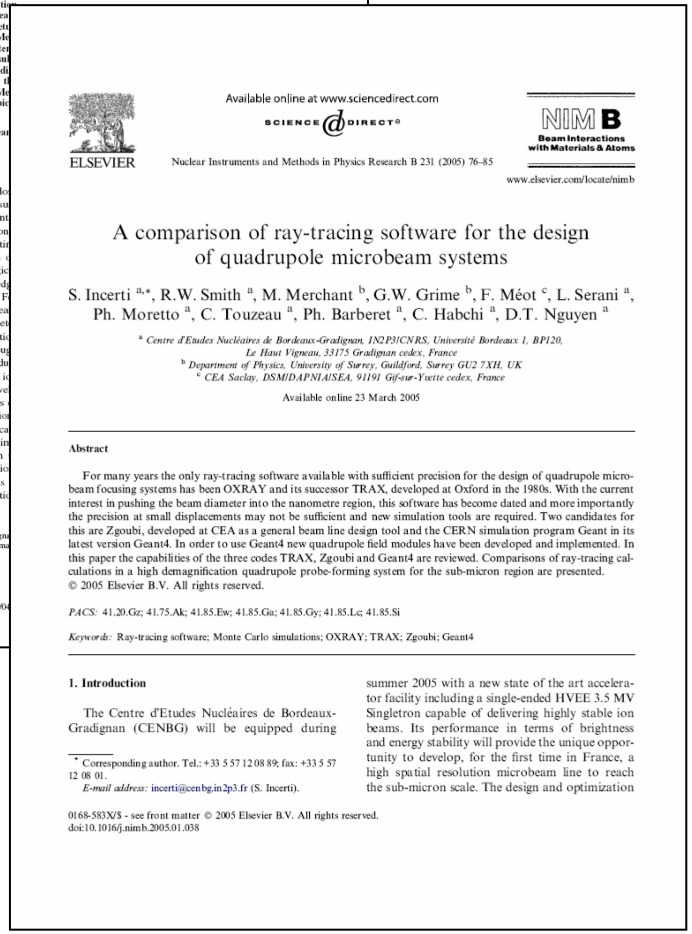
Centre d'Etudes Nucléaires de Bordeaux-Gradignan, IN2P3/CNRS, Université Bordeaux 1, BP120, Le Haut Vigneau, 33175 Gradignan cedex, France



IEEE TRANSACTIONS ON NUCLEAR SCIENCE, VOL. 51, NO. 4, AUGUST 2004 1395

Simulation of Cellular Irradiation With the CENBG Microbeam Line Using GEANT4

Sébastien Incerti, P. Barberet, R. Villeneuve, P. Aguer, E. Gontier, C. Michelet-Habchi, P. Moretto, D. T. Nguyen, T. Pouthier, and R. W. Smith



Nuclear Instruments and Methods in Physics Research B 231 (2005) 76–85

A comparison of ray-tracing software for the design of quadrupole microbeam systems

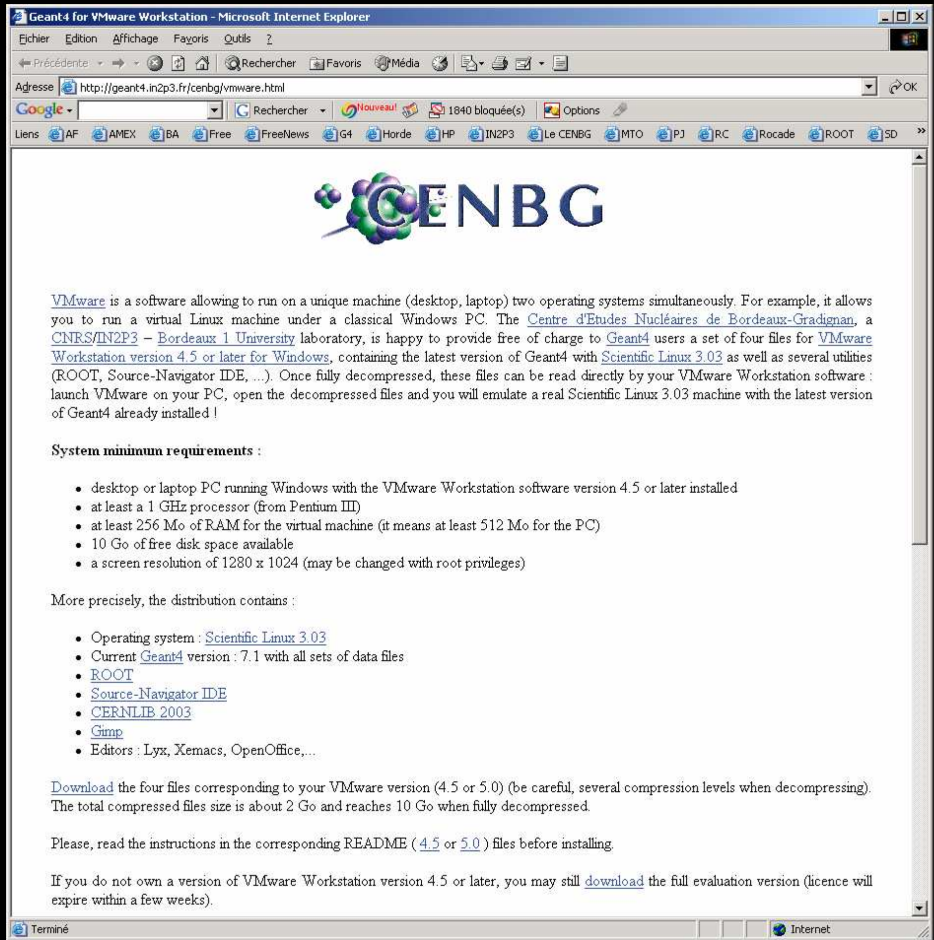
S. Incerti [a,*], R.W. Smith [a], M. Merchant [b], G.W. Grime [b], F. Méot [c], L. Serani [a], Ph. Moretto [a], C. Touzeau [a], Ph. Barberet [a], C. Habchi [a], D.T. Nguyen [a]

Abstract

For many years the only ray-tracing software available with sufficient precision for the design of quadrupole microbeam focusing systems has been OXRAY and its successor TRAX, developed at Oxford in the 1980s. With the current interest in pushing the beam diameter into the nanometre region, this software has become dated and more importantly the precision at small displacements may not be sufficient and new simulation tools are required. Two candidates for this are Zgoubi, developed at CEA as a general beam line design tool and the CERN simulation program Geant in its latest version Geant4. In order to use Geant4 new quadrupole field modules have been developed and implemented. In this paper the capabilities of the three codes TRAX, Zgoubi and Geant4 are reviewed. Comparisons of ray-tracing calculations in a high demagnification quadrupole probe-forming system for the sub-micron region are presented.

- Nucl.Instrum.Meth.B231:76-85,2005
- IEEE Trans.Nucl.Sci.51:1395-1401,2004
- Nucl.Instrum.Meth.B210:92-97,2003

Making Geant4 easily available : VMware



VMware is a software allowing to run on a unique machine (desktop, laptop) two operating systems simultaneously. For example, it allows you to run a virtual Linux machine under a classical Windows PC. The Centre d'Etudes Nucléaires de Bordeaux-Gradignan, a CNRS/IN2P3 – Bordeaux 1 University laboratory, is happy to provide free of charge to Geant4 users a set of four files for VMware Workstation version 4.5 or later for Windows, containing the latest version of Geant4 with Scientific Linux 3.03 as well as several utilities (ROOT, Source-Navigator IDE, ...). Once fully decompressed, these files can be read directly by your VMware Workstation software : launch VMware on your PC, open the decompressed files and you will emulate a real Scientific Linux 3.03 machine with the latest version of Geant4 already installed !

System minimum requirements :

- desktop or laptop PC running Windows with the VMware Workstation software version 4.5 or later installed
- at least a 1 GHz processor (from Pentium III)
- at least 256 Mo of RAM for the virtual machine (it means at least 512 Mo for the PC)
- 10 Go of free disk space available
- a screen resolution of 1280 x 1024 (may be changed with root privileges)

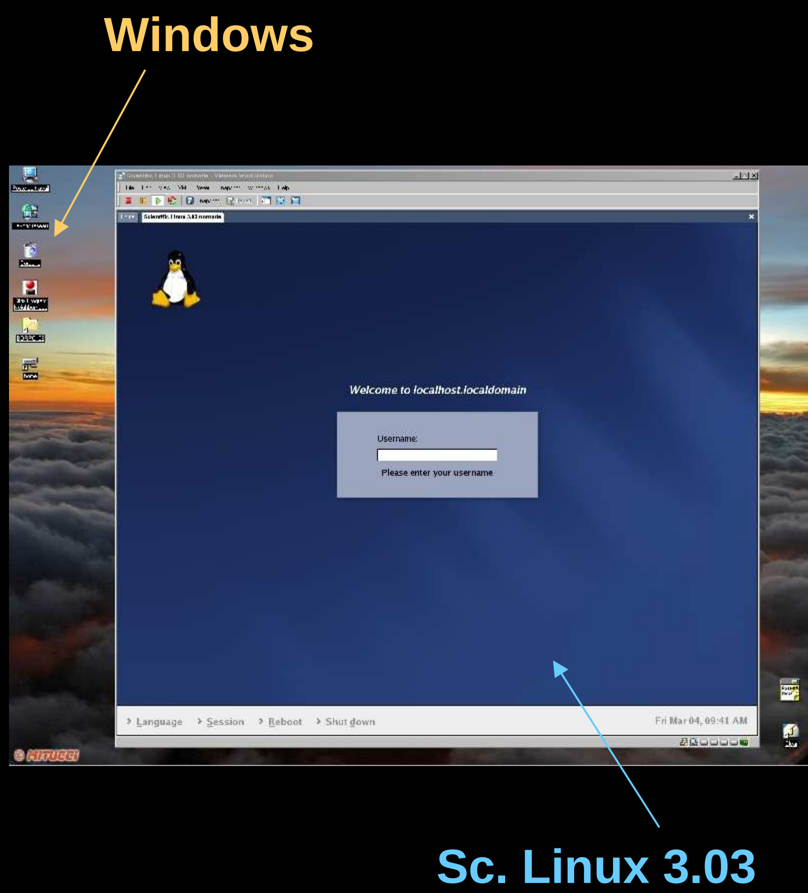
More precisely, the distribution contains :

- Operating system : Scientific Linux 3.03
- Current Geant4 version : 7.1 with all sets of data files
- ROOT
- Source-Navigator IDE
- CERNLIB 2003
- Gimp
- Editors : Lyx, Xemacs, OpenOffice,...

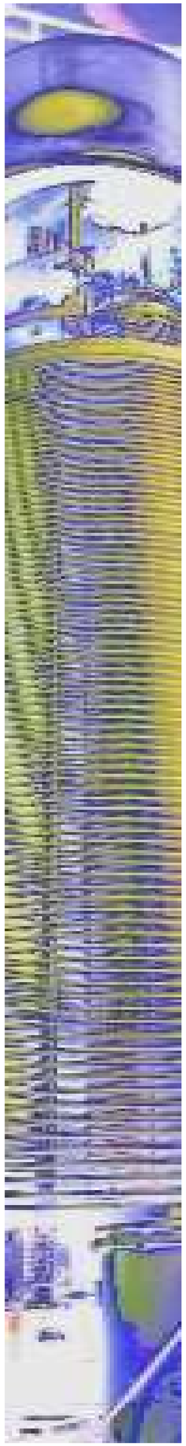
Download the four files corresponding to your VMware version (4.5 or 5.0) (be careful, several compression levels when decompressing). The total compressed files size is about 2 Go and reaches 10 Go when fully decompressed.

Please, read the instructions in the corresponding README (4.5 or 5.0) files before installing.

If you do not own a version of VMware Workstation version 4.5 or later, you may still download the full evaluation version (licence will expire within a few weeks).



http://geant4.in2p3.fr/cenbg/vmware.html



Thank you for your attention !