Geant4 for Hadrontherapy: status and challenges

G. Petringa, G.A.P. Cirrone, F. Farokhi, L. Pandola, M.A. Cortes-Giraldo, S.Guatelli

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Main Challenges in hadrontherapy

Physical

- Range uncertainity
- Accuracy of beam delivery

Biological

- Radiobiology issues
- New approaches

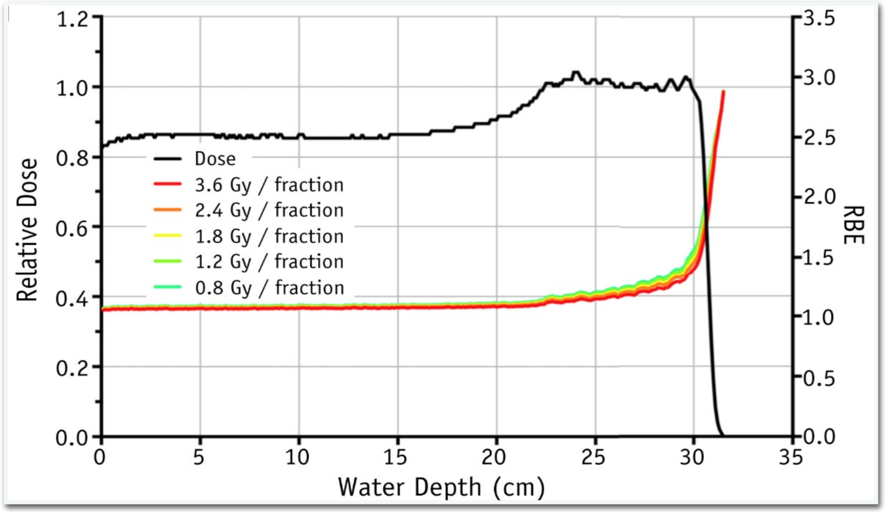
Where/how Geant4 can/could improve these issues ?

Radiobiology issues:
- RBE
- LET
- Fragmentation

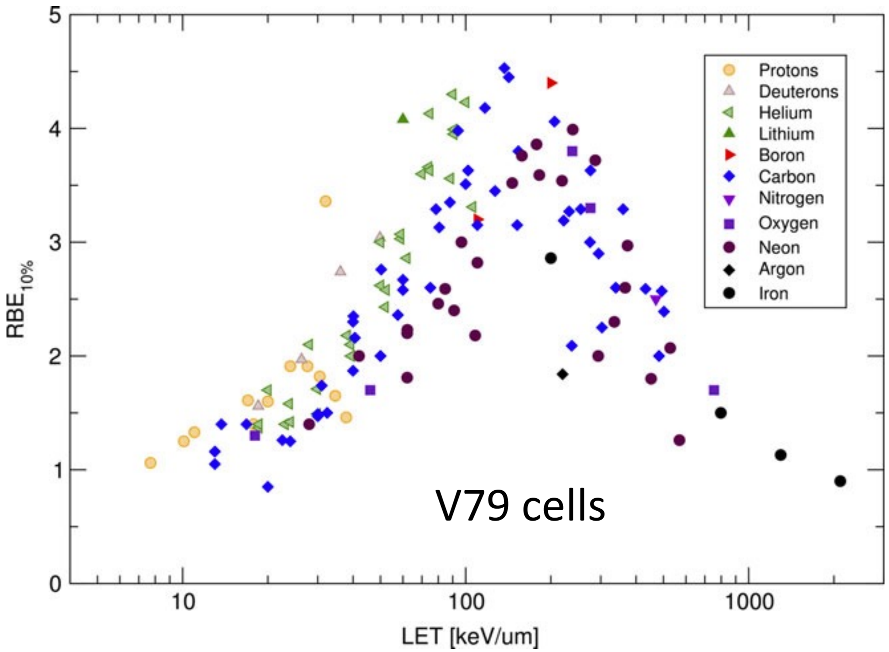
Relative Biological Effectiveness

Estimation of the biological damage along dose profile: which RBE should we use?

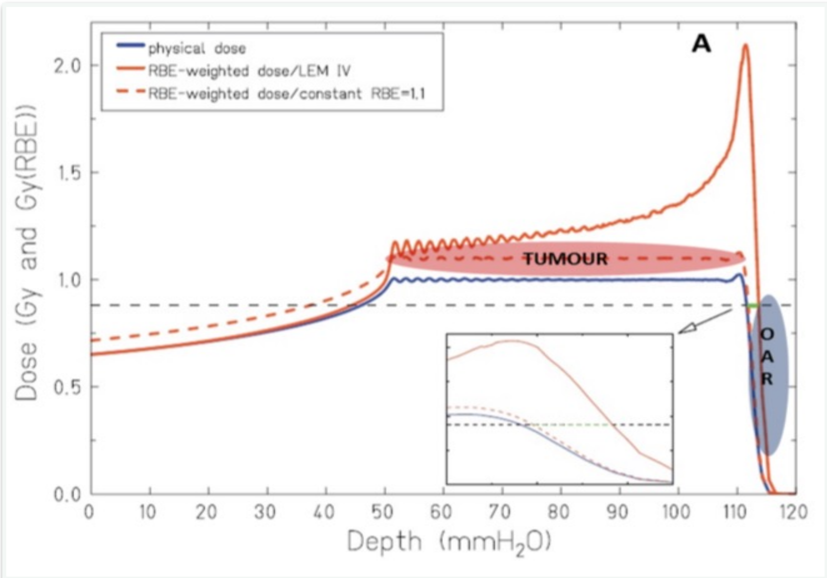
A key role is played by the average LET that is directly connected to the RBE



T. Marshall et al. "Investigating the Implications of a Variable RBE on Proton Dose Fractionation Across a Clinical Pencil Beam Scanned Spread-Out Bragg Peak "International Journal of Radiation Oncology Biology Physics, Volume 95, Issue 1, 1 May 2016, Pages 70-77



Jan Schuemann et al. Computational models and tools, Medical Physics, 45 (11), November 2018



Relative Biological Effectiveness

5 Macroscopic approach

Computation Method coupling Geant4 to LEM/MKM

Generation of Look Up Table based on LEM or MKM (Survival code) → Mixed Field calculation → Survival Fraction

$$\langle \alpha_D \rangle = \frac{\sum_i \alpha_{D_i} \cdot D_i}{\sum_i D_i}$$

$$\langle \beta_D \rangle = \left(\frac{\sum_i \sqrt{\beta_{D_i}} \cdot D_i}{\sum_i D_i}\right)^2$$

Mixed Field calculation

$$SF = e^{-(\langle \alpha_D \rangle D + \langle \beta_D \rangle D^2)}$$

Survival Fraction

Contents lists available at ScienceDirect

Physica Medica

journal homepage: www.elsevier.com/locate/ejmp

Original paper

Radiobiological quantities in proton-therapy: Estimation and validation using Geant4-based Monte Carlo simulations

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[d] INFN-NA, Istituto Nazionale di Fisica Nucleare, Sezione di Napoli, Complesso Universitario di M. S. Angelo, Via Cintia, I-80126 Napoli, Italy
[e] INFN-TO, Istituto Nazionale di Fisica Nucleare, Sezione di Torino, Torino, Italy
[f] IBFM-CNR, Institute of Molecular Bioimaging and Physiology – National Research Council, Cefalù, PA, Italy
[g] ELI-Beamline Project, Inst. Physics, ASCR, PALS Center, Prague, Czech Republic
[h] National Physical Laboratory, Acoustic and Ionizing Radiation Division, Teddington TW11 0LW, Middlesex, UK

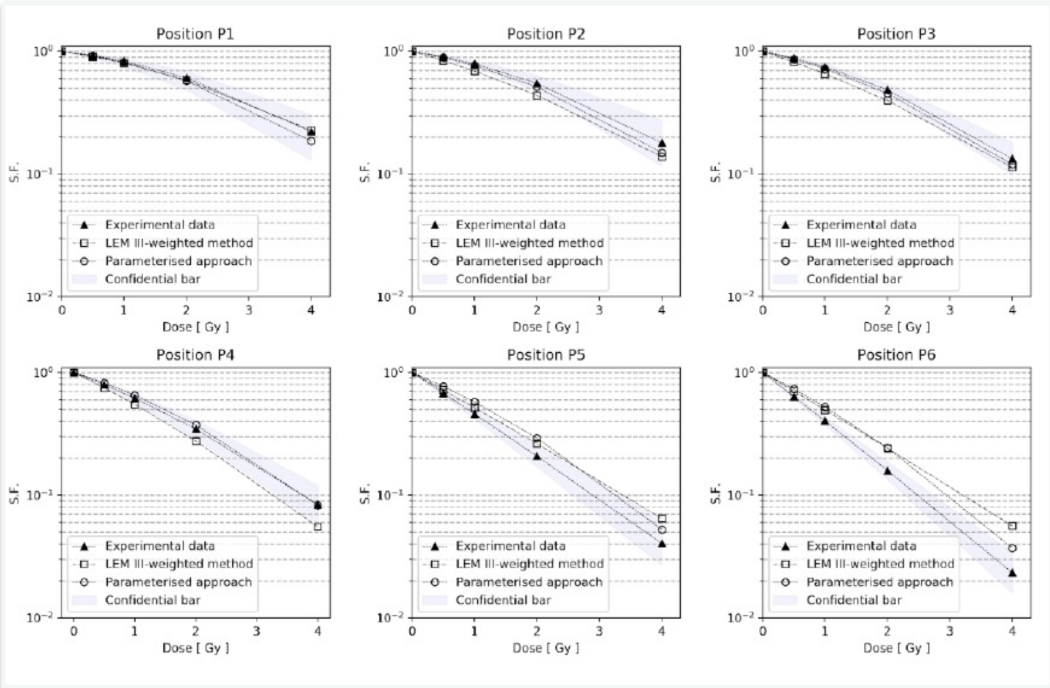
applied sciences

MDPI

Article

Radiobiological Outcomes, Microdosimetric Evaluations and Monte Carlo Predictions in Eye Proton Therapy

Giada Petringa[1,2,†], Marco Calvaruso[1,3,*], Valeria Conte[4], Pavel Bláha[5], Valentina Bravatà[1,3], Francesco Paolo Cammarata[1,3], Giacomo Cuttone[1,6], Giusi Irma Forte[1,3], Otilija Keta[7], Lorenzo Manti[5,8], Luigi Minafra[1,3], Vladana Petković[7], Ivan Petrović[7], Selene Richiusa[1,3], Aleksandra Ristić Fira[7], Giorgio Russo[1,3] and Giuseppe Antonio Pablo Cirrone[1,6,9,†]



Relative Biological Effectiveness

6 Microscopic approach

dnadamage1 & molecularDNA

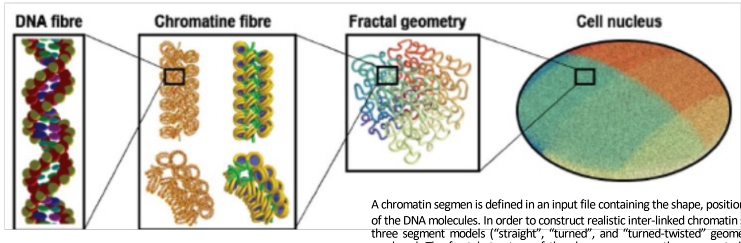
Moleculardna:
Macro files can control every aspect of the simulation.

```
/world/worldSize 10200 nm
/cell/radiusSize 3 3 3 um

/dnageom/setSmartVoxels 1
/dnageom/checkOverlaps false

/dnageom/radicalKillDistance 9 nm
/dnageom/interactionDirectRange 7 angstrom

/dnageom/placementSize 30 30 100 nm
/dnageom/fractalScaling 1 1 1 nm
/dnageom/definitionFile geometries/prisms200k_r3000.txt
/dnageom/placementVolume prism geometries/straight-216-0.txt

# Damage Model
/dnadamage/directDamageLower 17.5 eV
/dnadamage/directDamageUpper 17.5 eV

/dnadamage/indirectOHBaseChance 1.0
/dnadamage/indirectOHStrandChance 0.65
/dnadamage/inductionOHChance 0.0

/dnadamage/indirectHBaseChance 1.0
/dnadamage/indirectHStrandChance 0.65
/dnadamage/inductionHChance 0.00

/gps/particle e-
/gps/ang/type iso
/gps/energy 4.5 keV
/gps/pos/type Volume
/gps/pos/shape Sphere
/gps/pos/radius 500 nm
/gps/pos/centre 0 0 0 nm
/run/beamOn 1000
```

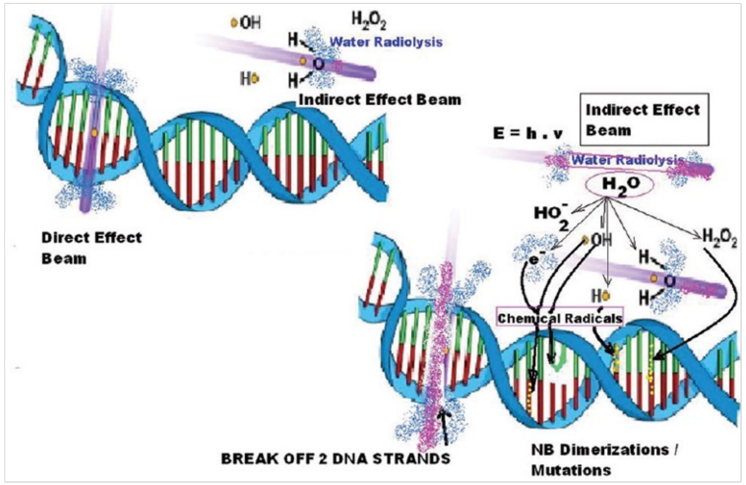
Geometry info

Damage model

Particle source

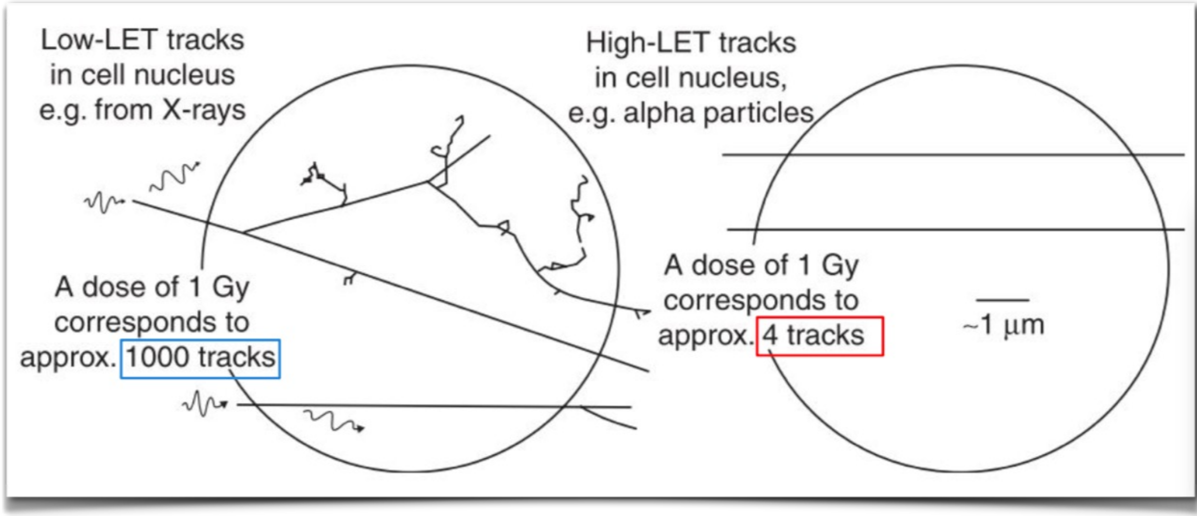


A chromatin segmen is defined in an input file containing the shape, position, and size of the DNA molecules. In order to construct realistic inter-linked chromatin segments, three segment models ("straight", "turned", and "turned-twisted" geometries) are produced. The fractal structure of the chromosome was then generated from the Hilbert curve, which is typically used for continuous fractal space-filling

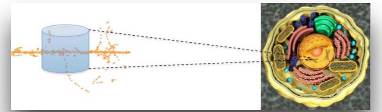


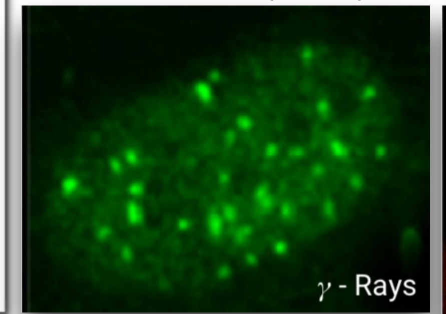
a simplified **human fibroblast cell** was evaluated using the proposed changes and compared with experimental data.
presented various quantities such as: **SSB/DSB ratio** as a function of LET, the **distribution of fragment lengths** and the **scavengeable fraction as a function of LET**.
time evolution of damage within an analytical **repair model**
more accurate **electron elastic model**
calibrated pre-chemical and chemical parameters

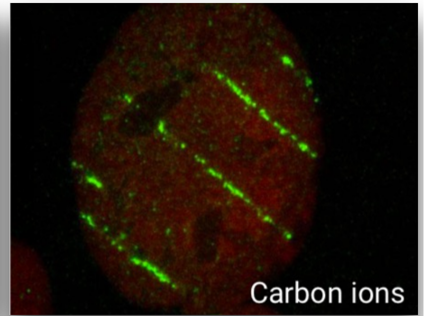
Linear Energy Transfer



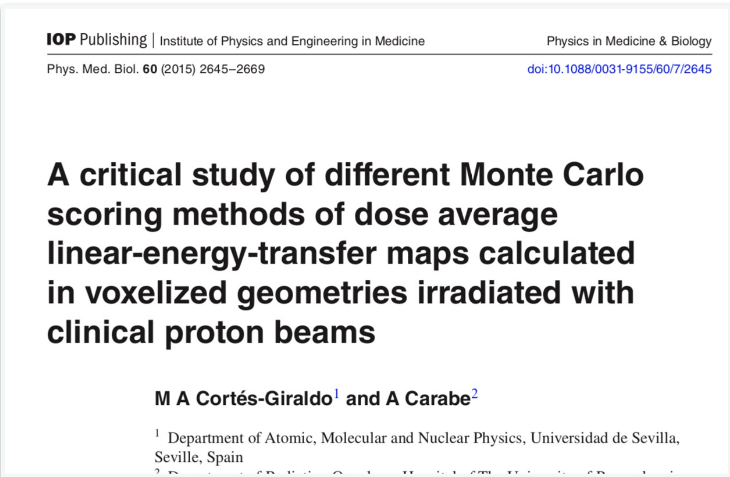
The biological damage is strictly related to the radiation quality







Which LET definition should we use ?


IOP Publishing | Institute of Physics and Engineering in Medicine — Physics in Medicine & Biology
Phys. Med. Biol. **60** (2015) 2645–2669 — doi:10.1088/0031-9155/60/7/2645

A critical study of different Monte Carlo scoring methods of dose average linear-energy-transfer maps calculated in voxelized geometries irradiated with clinical proton beams

M A Cortés-Giraldo[1] and A Carabe[2]

[1] Department of Atomic, Molecular and Nuclear Physics, Universidad de Sevilla, Seville, Spain

How much complicate is the LET calculation?

LET dose, LET track, LET only for primaries, LET also for secondaries, LET dependence on voxel, on production cut ….

Linear Energy Transfer

Several approaches

$$\bar{L}_\mathrm{d} = \int L\, d(L)\, \mathrm{d}L$$

$$\bar{L}_\mathrm{d} = \frac{\sum_n \left(\frac{\mathrm{d}E}{\mathrm{d}l}\right) \mathrm{d}E}{\sum_n \mathrm{d}E}$$

Method #1 (A)

$$\bar{L}_\mathrm{d} = \frac{\sum_{n=1}^{N} \sum_{s=1}^{S_n} \omega_n \frac{\varepsilon_{sn}^2}{l_{sn}}}{\sum_{n=1}^{N} \sum_{s=1}^{S_n} \omega_n\, \varepsilon_{sn}}$$

Step-by-step computation of the actual **dE/dl** of each proton

- ω = track weight
- ε = electronic energy loss per step(*)
- l = step length

(*) Kinetic energy of all secondary electrons included in ε (unrestricted LET)

Method #2 (B)

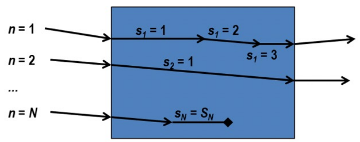
$$\bar{L}_\mathrm{d} = \frac{\sum_{n=1}^{N} \left[\omega_n \frac{\left(\sum_{s=1}^{S_n} \varepsilon_{sn}\right)^2}{\sum_{s=1}^{S_n} l_{sn}} \right]}{\sum_{n=1}^{N} \left[\omega_n \sum_{s=1}^{S_n} \varepsilon_{sn} \right]}$$

Computation along the voxel of the actual **dE/dl** of each proton

Method #3 (C)

$$\bar{L}_\mathrm{d} = \frac{\sum_{n=1}^{N} \sum_{s=1}^{S_n} \omega_n\, L_{sn}\, \varepsilon_{sn}}{\sum_{n=1}^{N} \sum_{s=1}^{S_n} \omega_n\, \varepsilon_{sn}}$$

L_{sn} is the ***average*** **dE/dl** (i.e., obtained from tables) according to particle energy and material (step-by-step computation)



Romano F. et al. Phys.Med.Bio. 59 (2014)

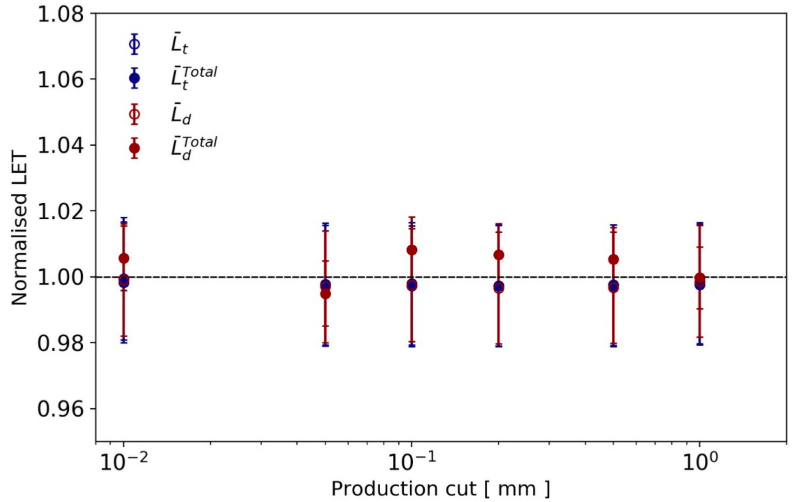
Cortes M.G. et al. Phys.Med.Bio. 60 (2015)

Guan F. et al. Medical Physics (2015)

Petringa G. et al. Phys.Med.Bio. 65 (2020)

main dependences:

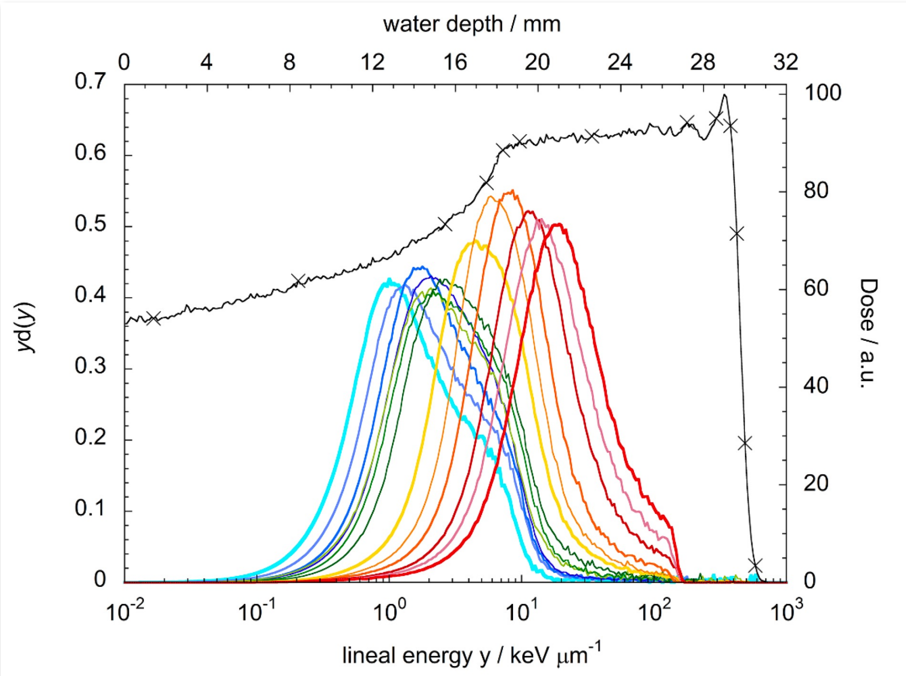
- ☑ production cut
- ☑ voxel size
- ☑ step size

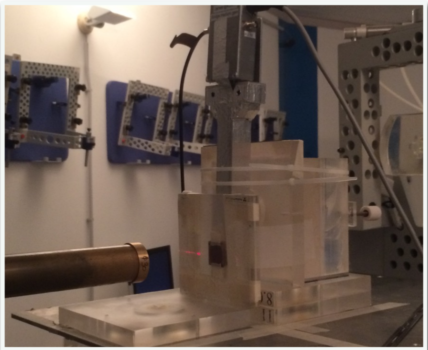


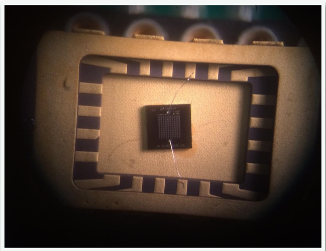
Thanks to M.A.Cortes-Giraldo

Linear Energy Transfer

9 microdosimetric point of view

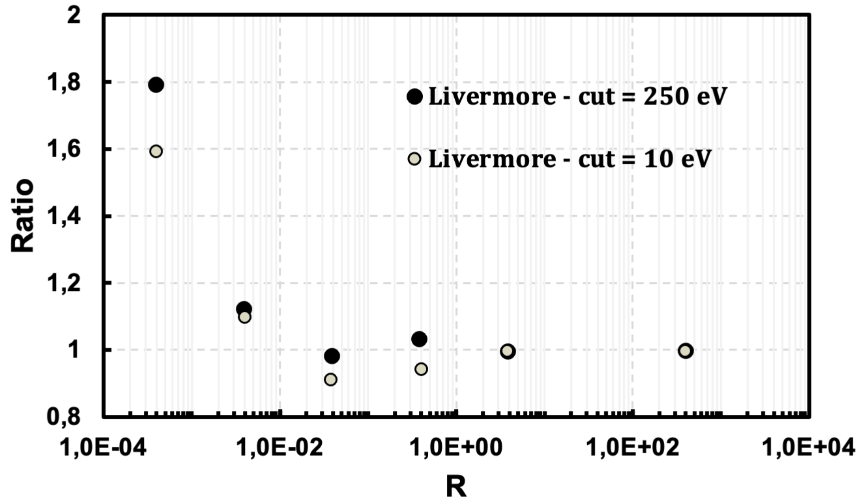






active volume:
um - nm scale

depending on the physical size and density of the *Sensitive Volume* and of the incident radiation field considered, a Track Structure approach may be more adequate for microdosimetry



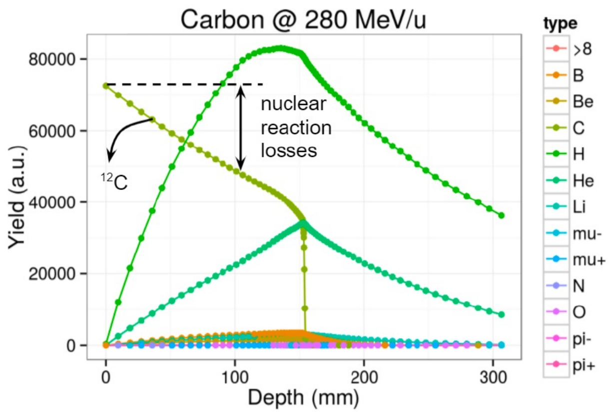
P Lazarakis *et al* 2018 *Biomed. Phys. Eng. Express* 4 024001

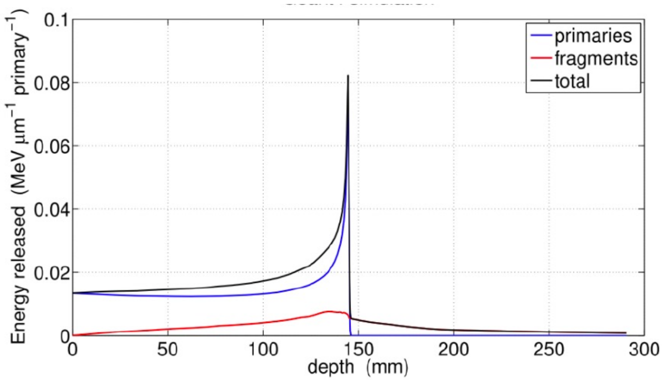
Ratio of the energy deposition calculated in the Sensitive Volume by means of Geant4 CH physics models and Geant4-DNA. R is the ratio of the variable SV diameter and the average track length of incident 10 keV electrons.

Target and Projectile fragmentation

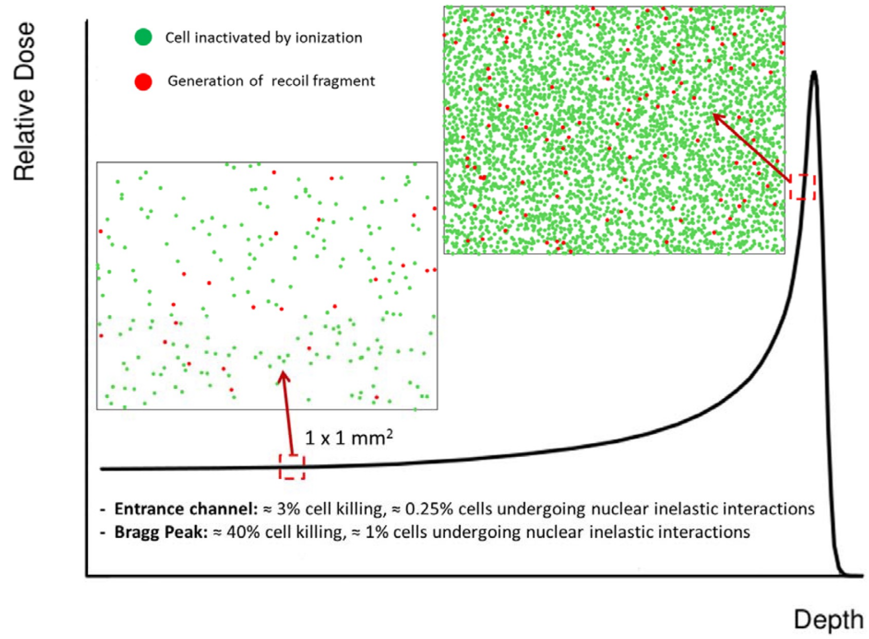
In the case of an ion beam irradiation with high Z ($Z \gtrsim 2$) the projectile fragments play the major role, while for proton beams a potentially non negligible dose enhancement can be observed due to the presence of target fragments.

Projectile fragmentation





Target fragmentation



F. Tommasino & M.Durante, Cancers 2015, 7

Target and Projectile fragmentation

A limitation is currently represented by the limited set of nuclear reaction cross sections on which Monte Carlo codes rely

FramentatiOn Of Target

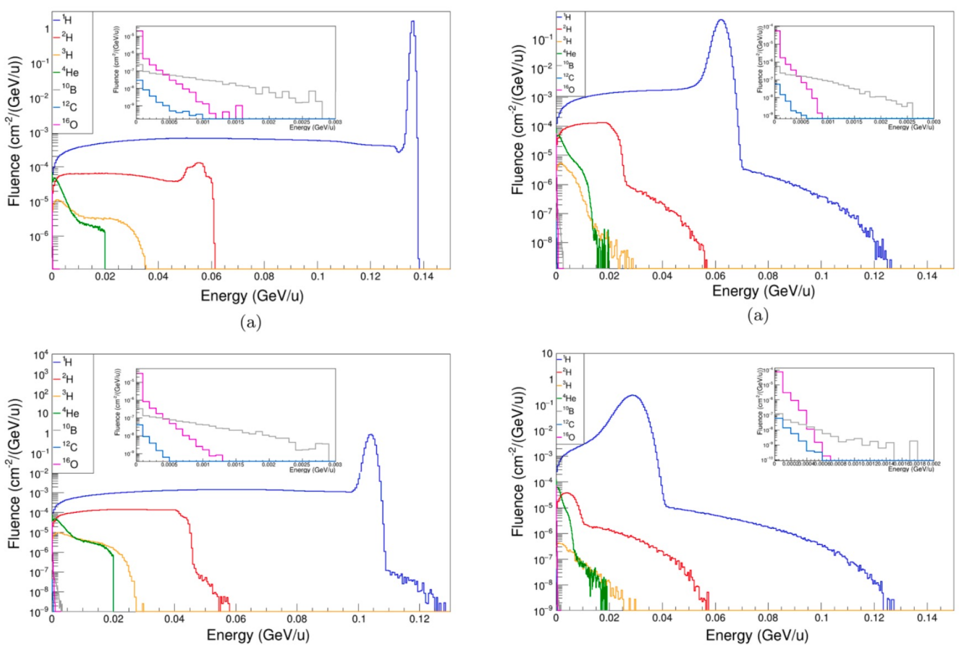
The detection of low energetic fragments, secondary protons and fragments, is challenging due to their very short range

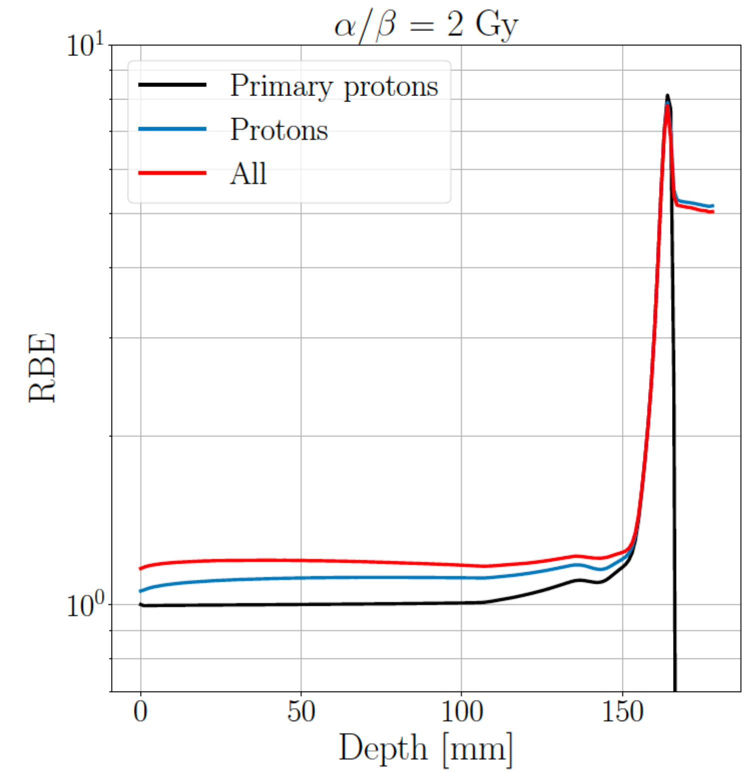
cancers MDPI

Article

Biological Impact of Target Fragments on Proton Treatment Plans: An Analysis Based on the Current Cross-Section Data and a Full Mixed Field Approach

Elettra Valentina Bellinzona [1,2], Leszek Grzanka [3], Andrea Attili [4], Francesco Tommasino [1,2], Thomas Friedrich [5], Michael Krämer [5], Michael Scholz [5], Giuseppe Battistoni [2], Alessia Embriaco [6], Davide Chiappara [7,†], Giuseppe A. P. Cirrone [7], Giada Petringa [7,‡], Marco Durante [5,8] and Emanuele Scifoni [1,2,*]





Target and Projectile fragmentation

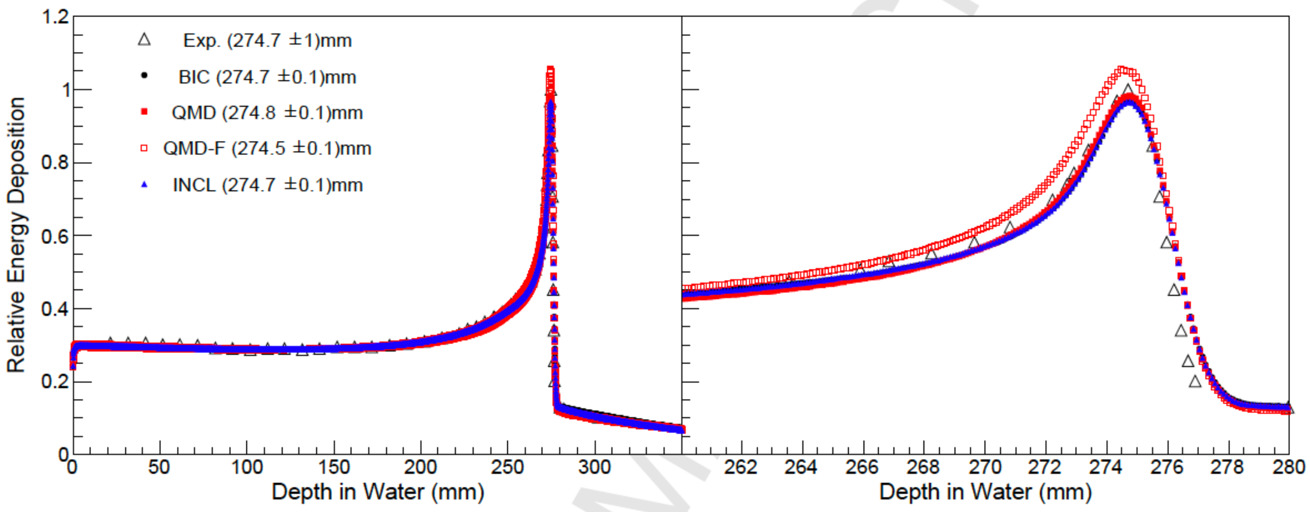
A limitation is currently represented by the limited set of nuclear reaction cross sections on which Monte Carlo codes rely

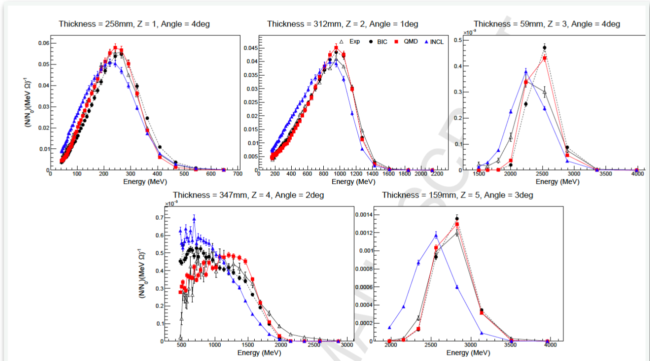
The detection of low energetic fragments, is challenging due to their very short range

ELSEVIER
Nuclear Instruments and Methods in Physics Research Section A: Accelerators, Spectrometers, Detectors and Associated Equipment
Volume 869, 11 October 2017, Pages 68-75

Validation of Geant4 fragmentation for Heavy Ion Therapy

David Bolst [a], Giuseppe A.P. Cirrone [b], Giacomo Cuttone [b], Gunter Folger [c], Sebastien Incerti [d, e], Vladimir Ivanchenko [c, f], Tatsumi Koi [g], Davide Mancusi [h], Luciano Pandola [b], Francesco Romano [b, i], Anatoly B. Rosenfeld [a], Susanna Guatelli [a]



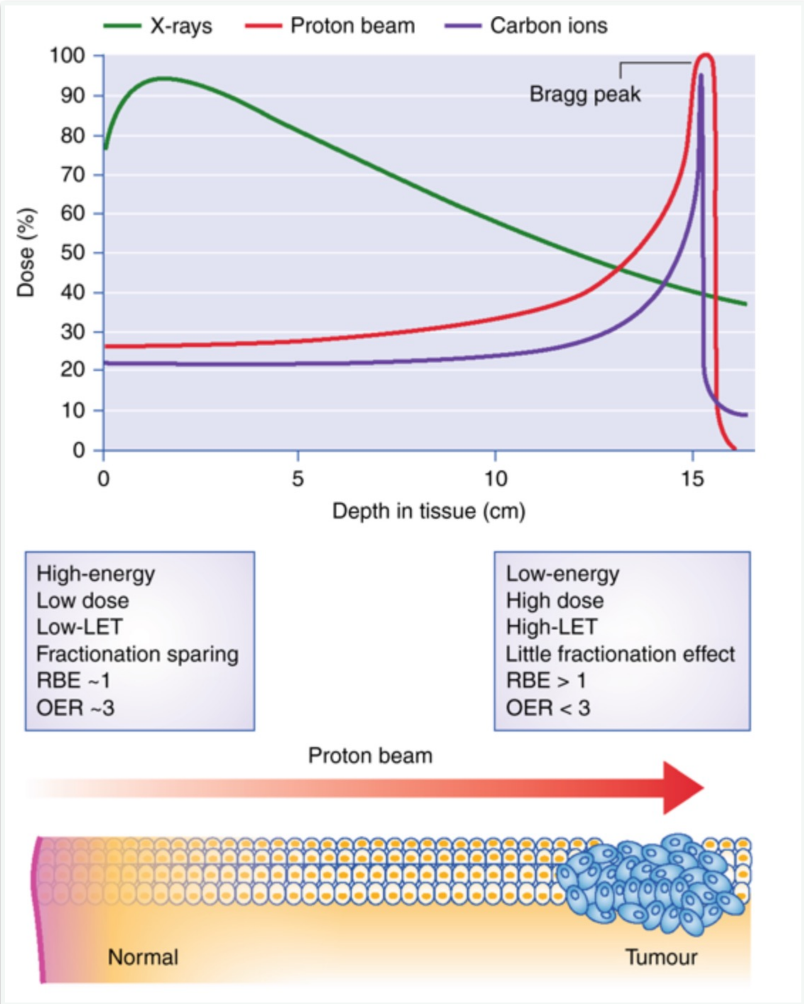


BIC, QMD and INCL++ models were benchmarked in Geant4 against experimental data for a pristine 400 MeV/u 12C ion beam founding an agreement within ~5%-35% compared to experimental values

New approaches:

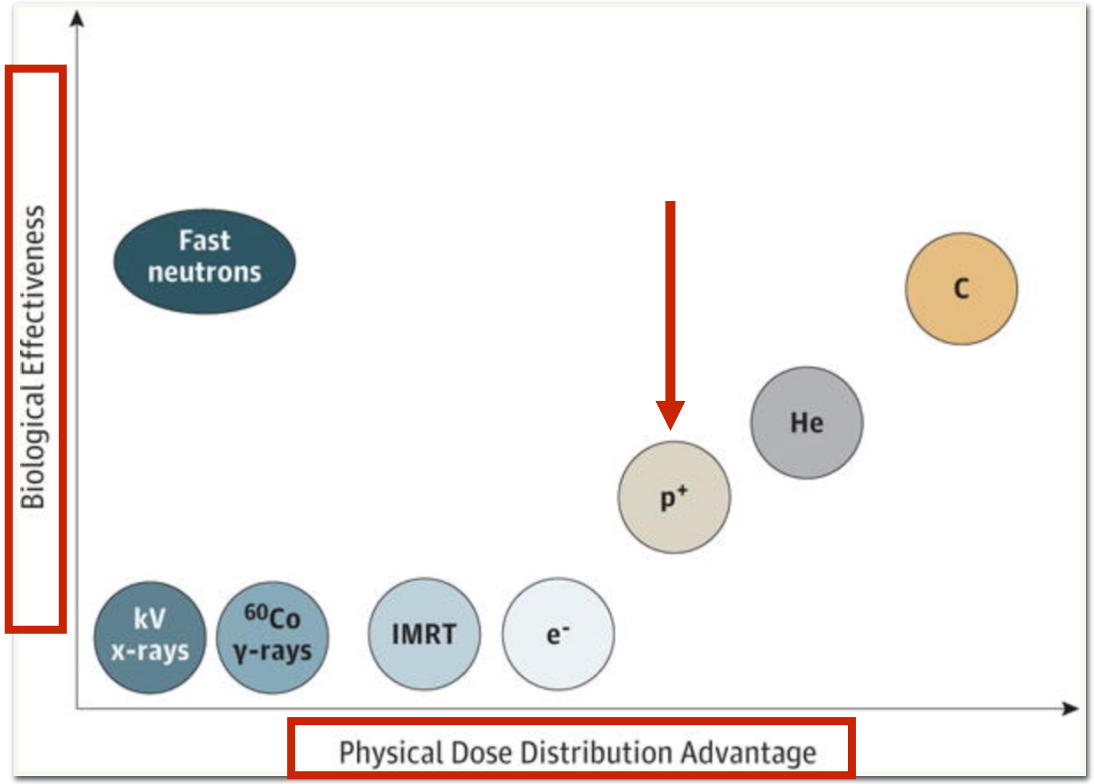
- Flash radiotherapy
- PBCT
- TAT and nanoparticles

Protontherapy: the rationale



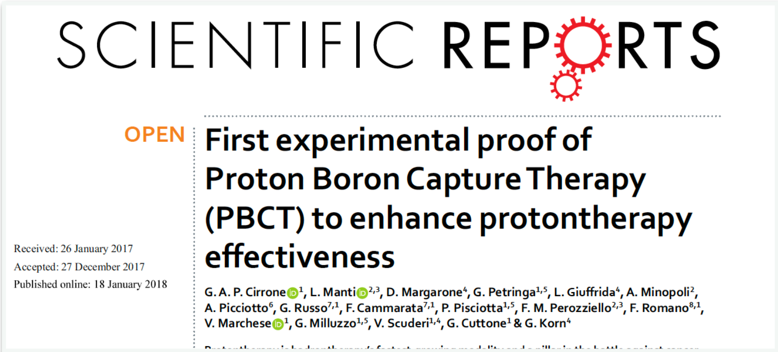
M. Durante, Proton Beam therapy in Europe, British Journal of Cancer, 777-778 (2019)

Focused research on protontherapy



A. Pomps, M. Durante and H. Choy, Heavy ions in cancer therapy, JAMA Oncol. 2016 2(12): 1539-1540.

Proton Boron Capture Therapy

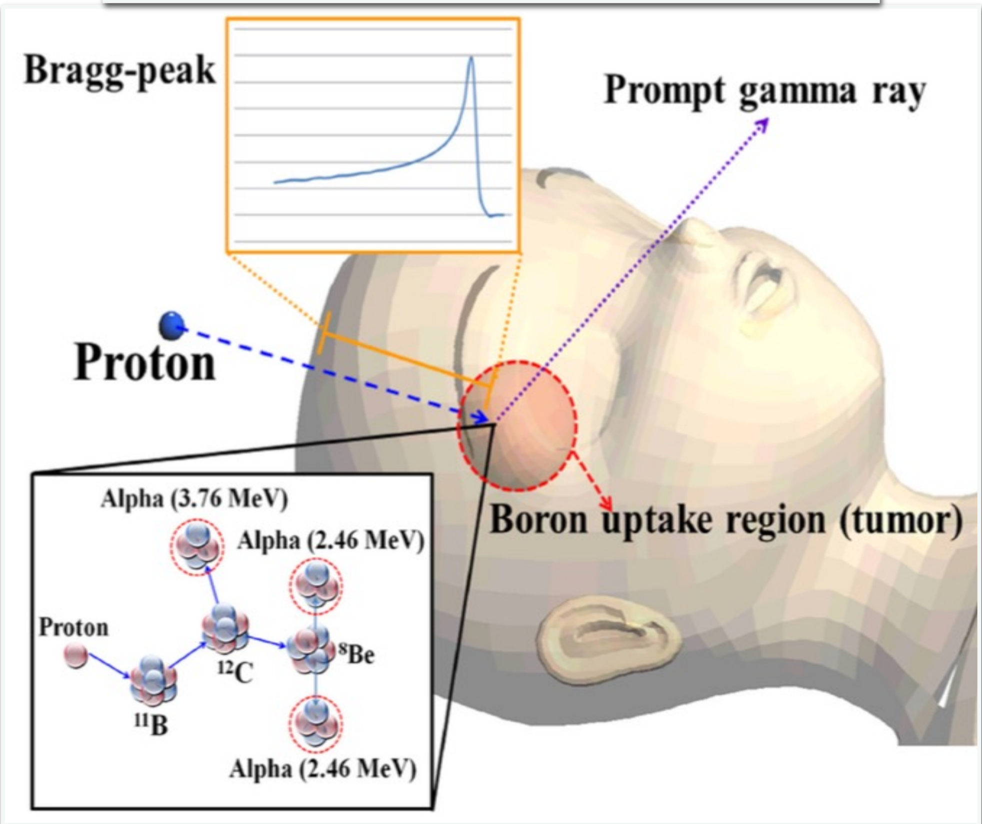

SCIENTIFIC REPORTS

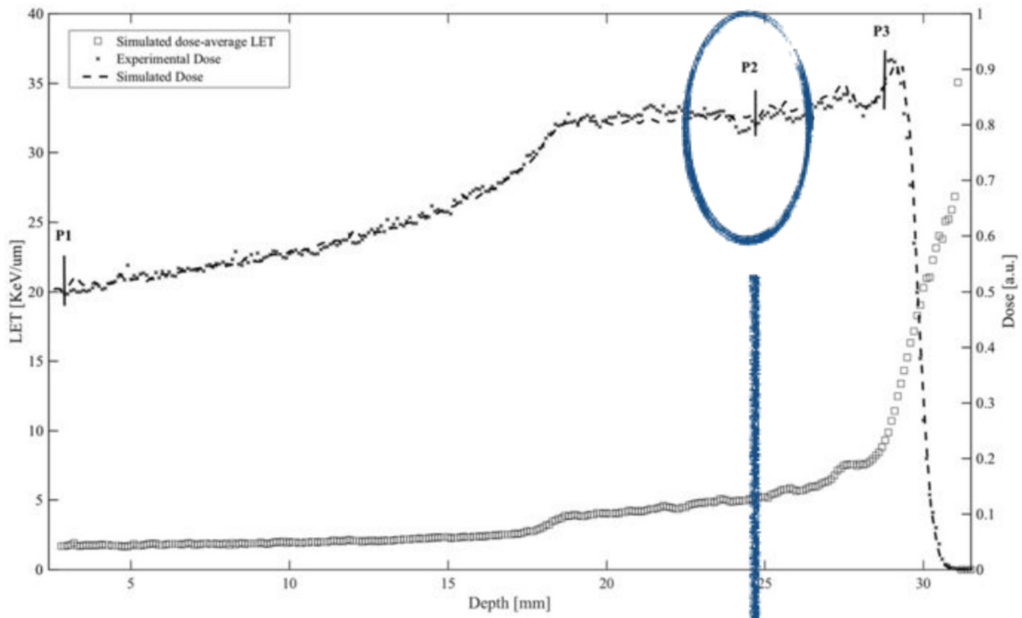
OPEN

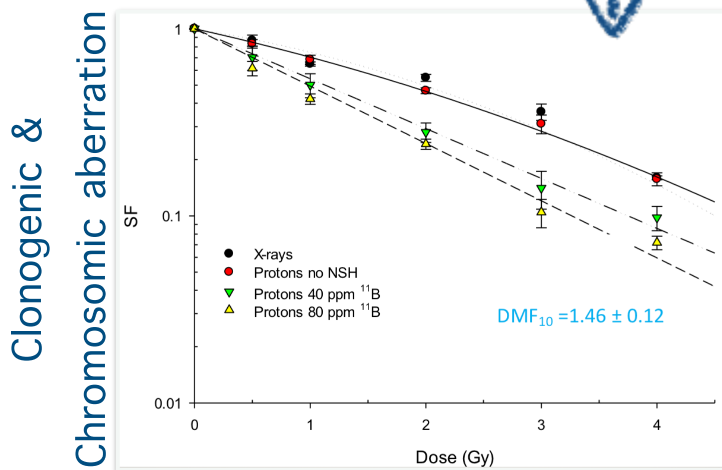
First experimental proof of Proton Boron Capture Therapy (PBCT) to enhance protontherapy effectiveness

Received: 26 January 2017
Accepted: 27 December 2017
Published online: 18 January 2018

G. A. P. Cirrone[1], L. Manti[2,3], D. Margarone[4], G. Petringa[1,5], L. Giuffrida[4], A. Minopoli[2], A. Picciotto[6], G. Russo[7,1], F. Cammarata[7,1], P. Pisciotta[1,5], F. M. Perozziello[2,3], F. Romano[8,1], V. Marchese[1], G. Milluzzo[1,5], V. Scuderi[1,4], G. Cuttone[1] & G. Korn[4]

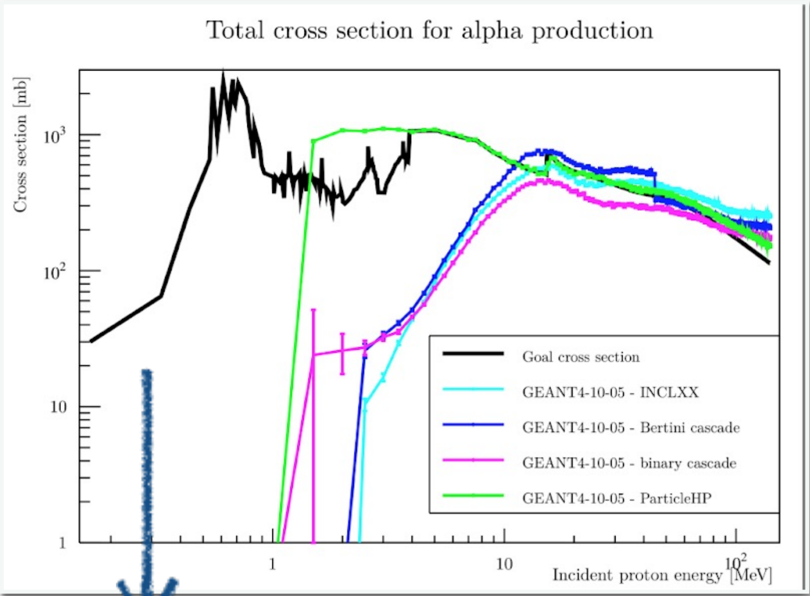


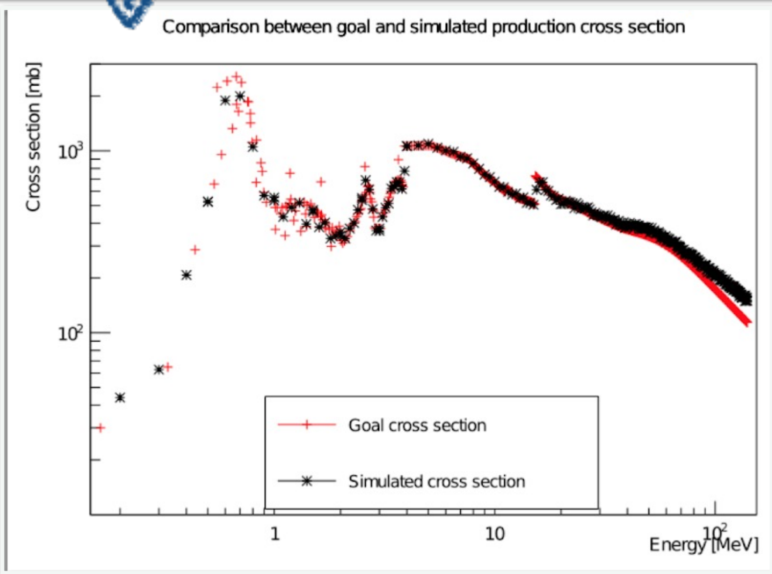


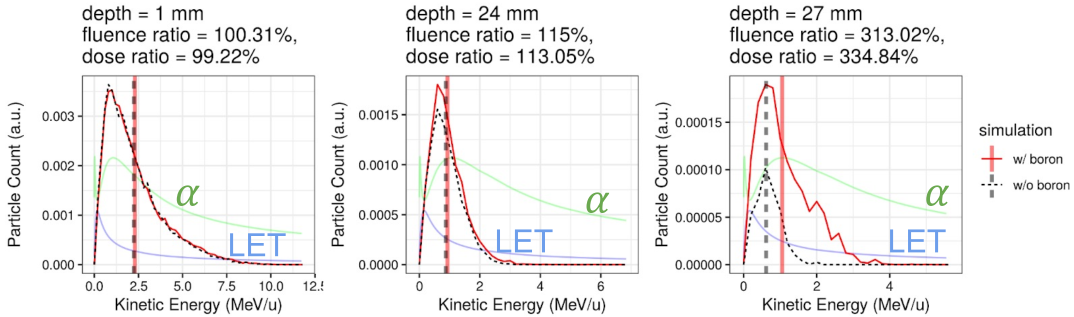


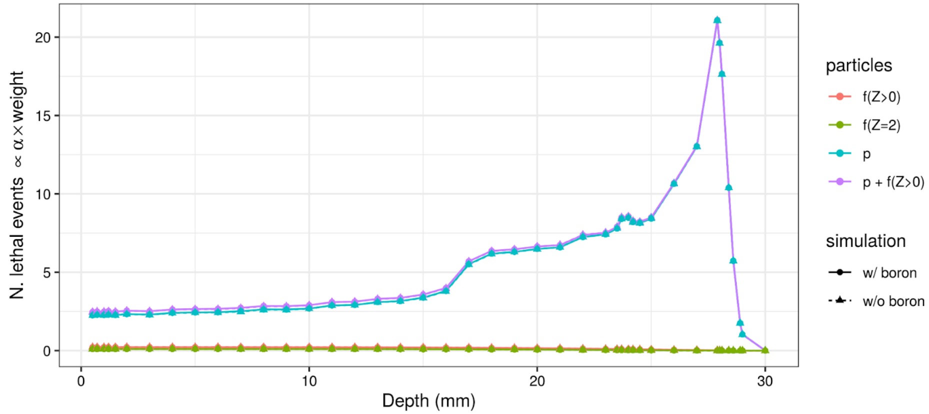
DMF_{10} (RBE_{10})= 1.46 ± 0.12

Proton Boron Capture Therapy



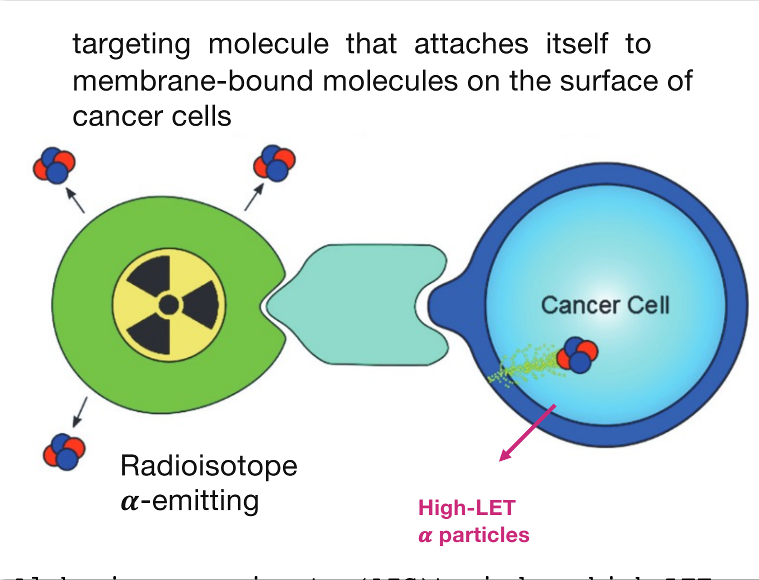






The effect is not detectable in a macroscopic scale (micrometres)
=> new studies are on going based on the extimation of the amount of radicals

Target Alpha Therapy



Alpha-immunoconjugate (AIC)to induce high-LET

particle emission

Barry J. Allen (2016)

The role of Monte Carlo code

Radioisotopes production;

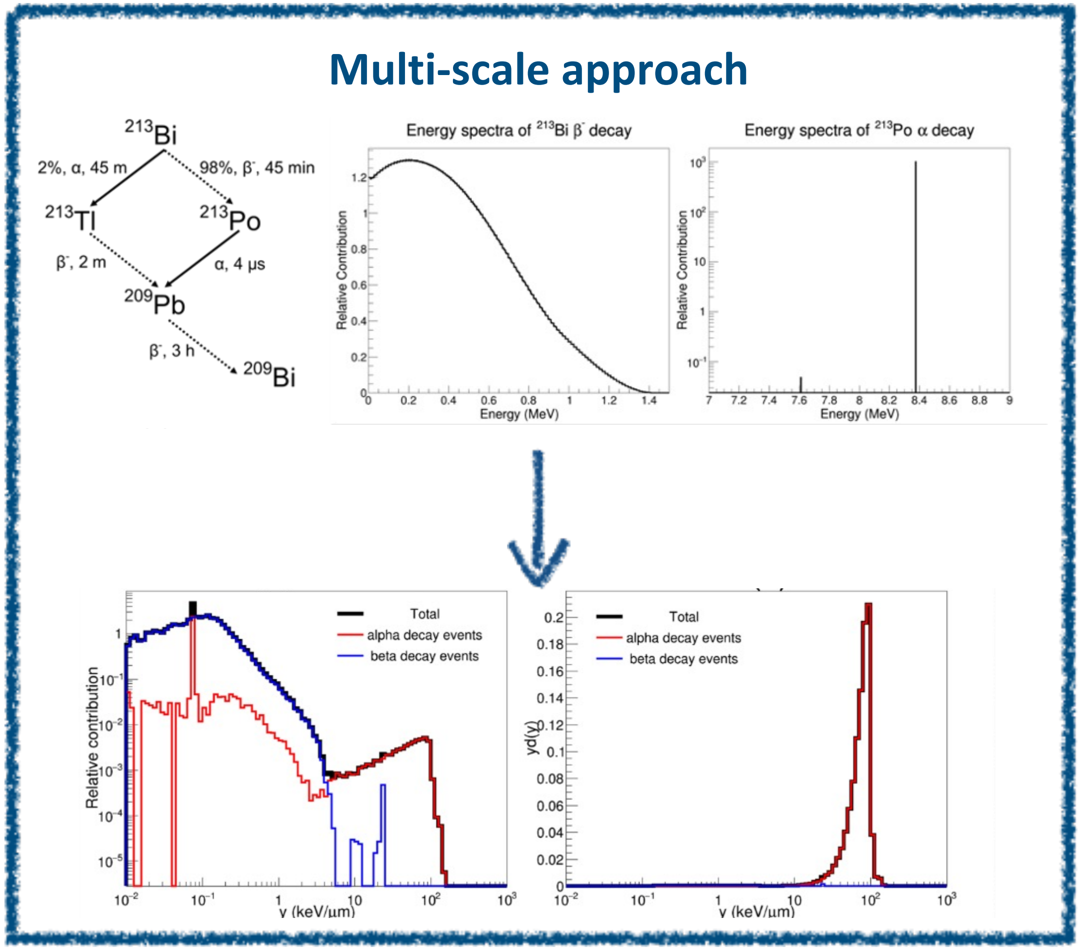
Simulation of quality assurance detectors;

Compton imaging;

Internal dosimetry;

Candidate TAT radioisotopes

^{212}Pb, ^{211}At, ^{213}Bi, ^{225}Ac, ^{233}Ra, ^{149}Tb, ^{227}Th

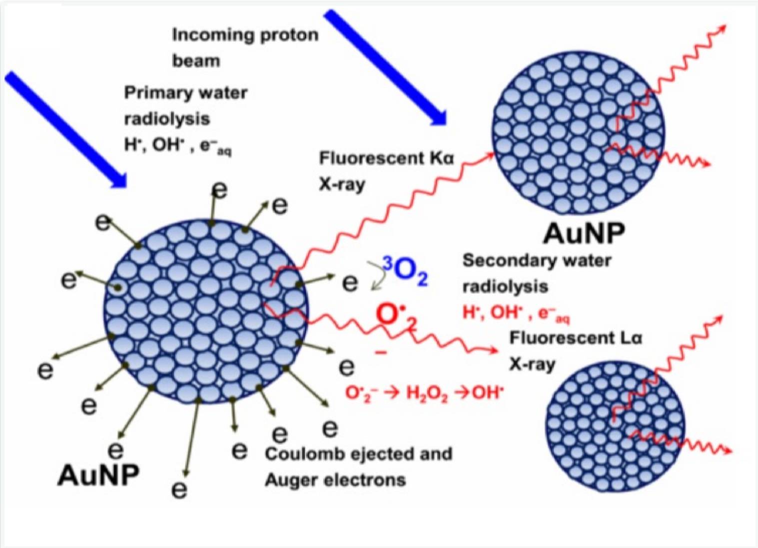


Thanks to Susanna Guatelli, David Bolst e Eva Bezak

Nanoparticles

Main advantages:

Toumor selectivity & Dose enhancement



AuNP emission activated by protons and secondary electrons and photons, and consecutive radical production. Kim et al (2012)

MC methods:

connection between micro- and nano-scale processes taking into account several radiobiological endpoints

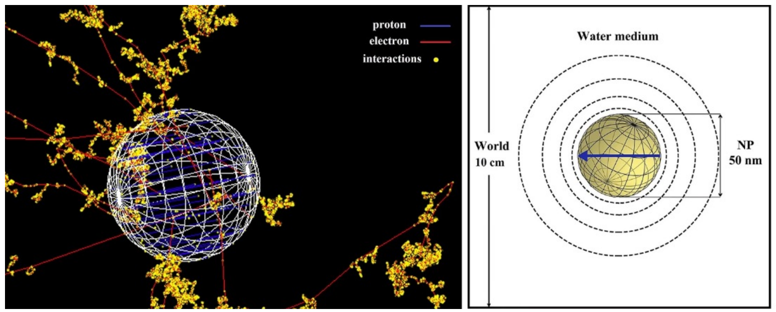
Physics models & biological damage

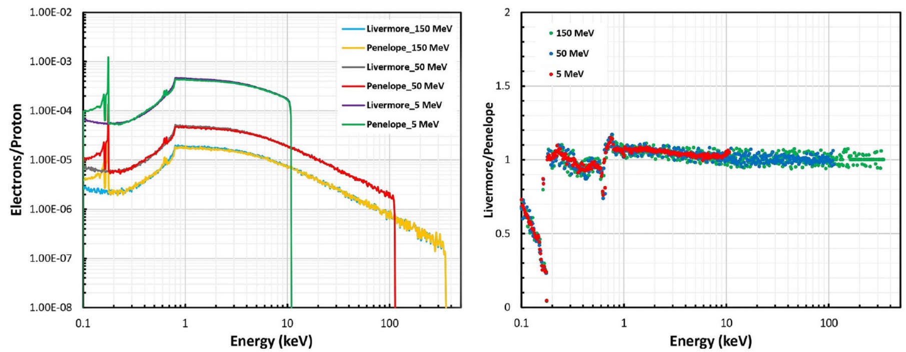
scientific reports

OPEN

Comparing Geant4 physics models for proton-induced dose deposition and radiolysis enhancement from a gold nanoparticle

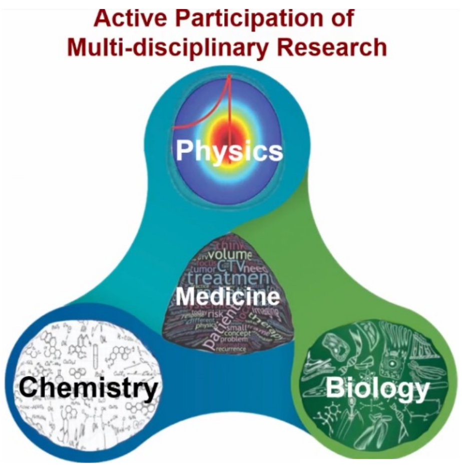
Saeed Rajabpour[1], Hassan Saberi[1], Javad Rasouli[2] & Nasrollah Jabbari[3]

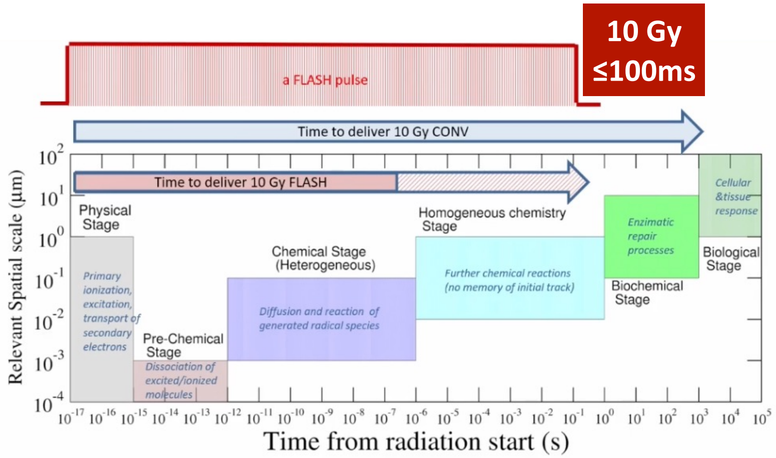




Flash radiotherapy

A promising new radiotherapy strategy to limit the toxicities and maintain the tumour control

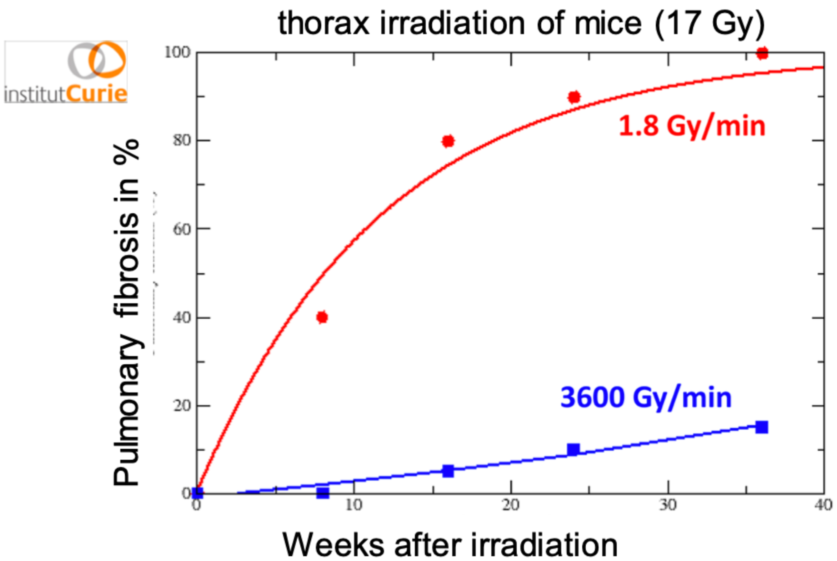




Weber, Scifoni, Durante Med Phys 2021 acc.

FLASH Factors:

- Dose
- Dose Rate
- LET?
- Tissue oxygen level
- Repair kinetics
- Biological endpoint
- ???

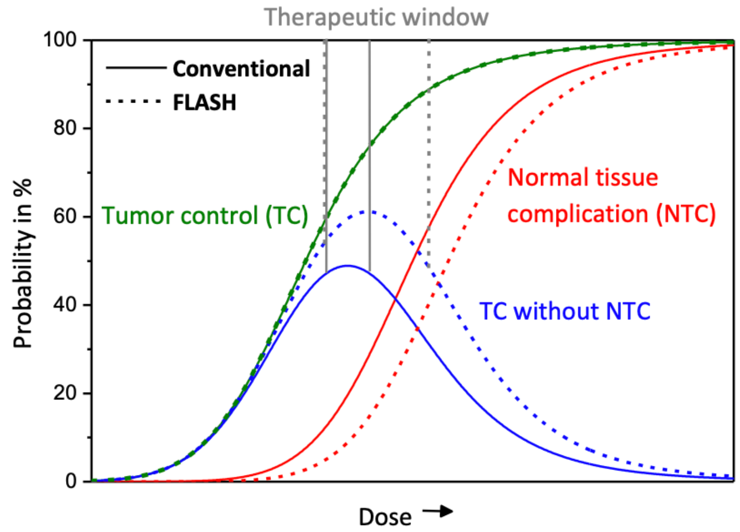


Favaudon et al., Sci Transl Med 6 (2014) 245ra93

Durante et al., Br J Radiol 91 (2018) 20170628

FLASH effect

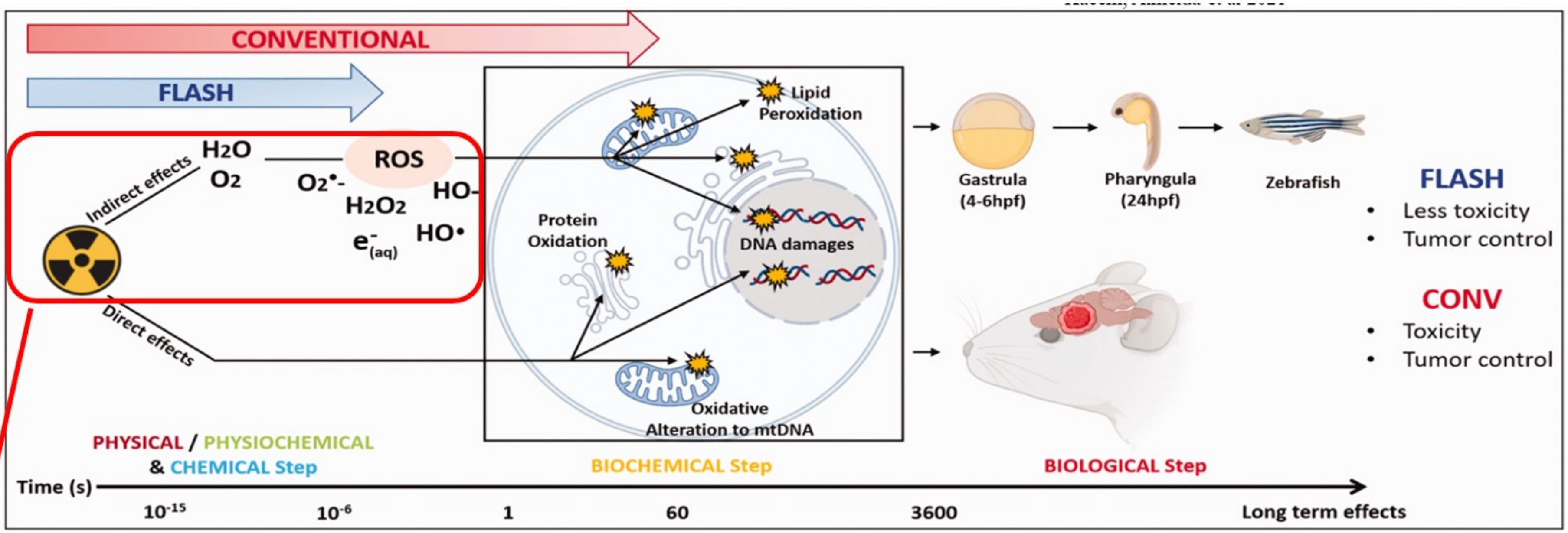
ultra-high dose rates



Flash radiotherapy

=> F.Farokhi "Evaluation of the effect of oxygen in Flash irradiation through Geant4-DNA"

20 Geant4-DNA and chemical stage



Geant4-DNA simulation (pre-chemical and chemical stages):

1. interaction of water radicals induced by particle irradiation
2. radiolytic production of reactive oxygen species (ROS)
3. **G-values** of different chemical species.

$$G = \frac{\text{Number of species}}{100\text{eV of deposited energy}}$$

&

Post processing:

1. **Calculation of Oxygen consumption**
2. **OER-weighted dose** calculation under dynamic oxygenation

⇩

To **evaluate the effect of oxygen** in FLASH irradiation, the result of **Geant4-DNA** simulation compared with the **TRAX-CHEM code**

→ S. Guatelli "Update on the G4-Med project and on the Geant4 Advanced Examples for medical applications"

→ F. Romano "Recent developments of Geant4 Advanced Examples for medical applications"