International School "Relativistic Heavy Ion Collisions, Cosmology and Dark Matter, Cancer Therapy" (15-26.05.2017) Oslo, May, 2017

Modeling ion-beam cancer therapy on macro and micro scales

Igor Mishustin[a,b]

in collaboration with Lucas Burigo[c], Igor Pshenichnov[a,d], Marcus Bleicher[a]

[a] *Frankfurt Institute for Advanced Studies, Frankfurt am Main*
[b] *National Research Center Kurchatov Institute, Moscow*
[c] *DeutschesKrebsforschungszentrum(DFLZ), Heidelberg*
[d] *Institute for Nuclear Research, RAS, Moscow*

FIAS Frankfurt Institute for Advanced Studies

HIC for FAIR Helmholtz International Center

RUSSIAN RESEARCH CENTRE KURCHATOV INSTITUTE

1. Introduction and motivation

- **Carbon-ion therapy serves as an advanced method to treat deeply seating tumors (brain, prostate, lungs).**
- **Due to the fragmentation of ^{12}C nuclei the beam is attenuated and secondary nuclear fragments form a complex radiation field.**
- **Such mixed radiation fields can be studied in experiments with Tissue-Equivalent Proportional Counters (TEPC) inside a water phantom.**
- **The radiation fields on micrometer scales can be modeled with MCHIT code based on the Geant4 toolkit.**

Monte Carlo modeling of hadron therapy

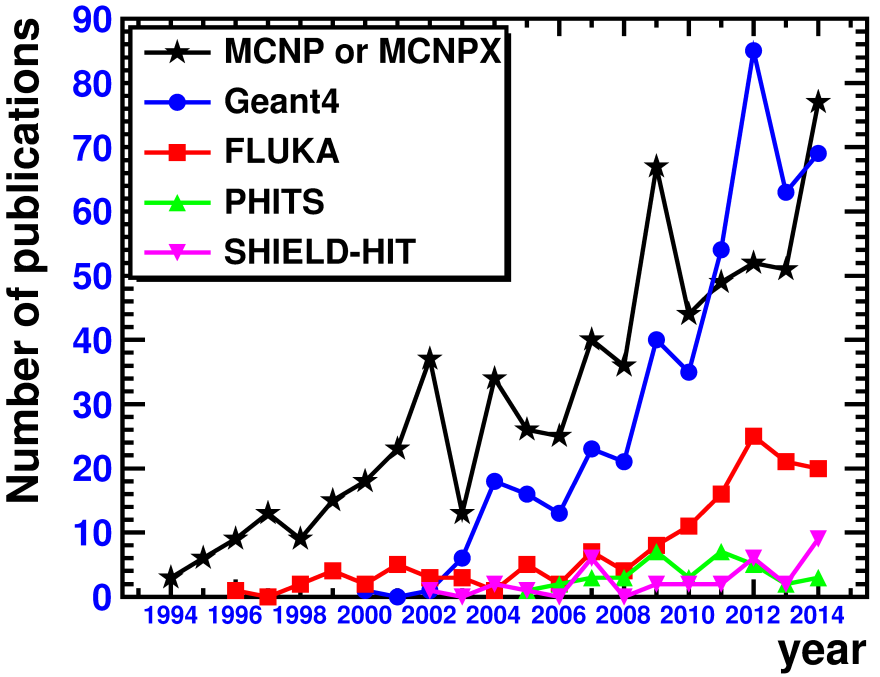
A set of various models is needed to simulate propagation and interaction of therapeutic ion beams in tissue-like media.

Now several general-purpose Monte Carlo particle transport codes (FLUKA, Geant4, MCNP, PHITS and SHIELD-HIT) are used for simulations in the field of hadron therapy.

For our study we decided to use models from open-access toolkit Geant4

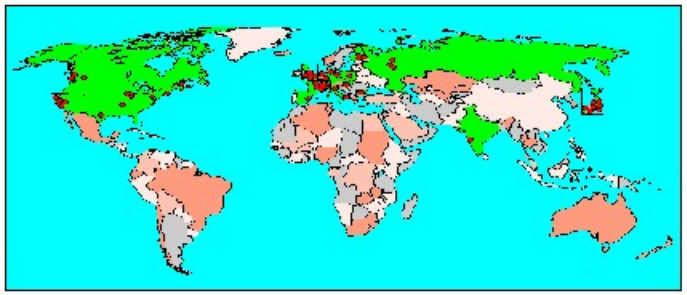
Annual number of publications in the field of hadron therapy, where respective Monte Carlo codes/tools were used.

Estimated from the Web of Science (Thomson Reuters) database 2015.



Geant4 is a rapidly developing toolkit for nuclear, particle, space and medical physics

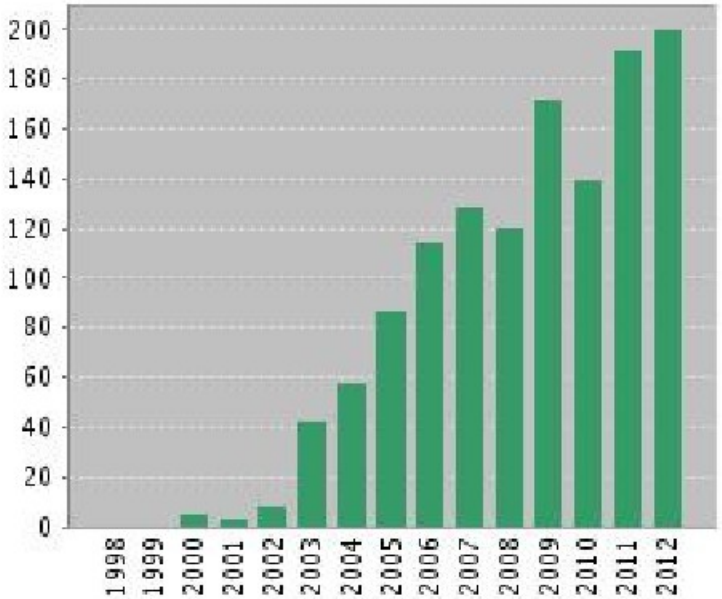
Geant4 collaboration

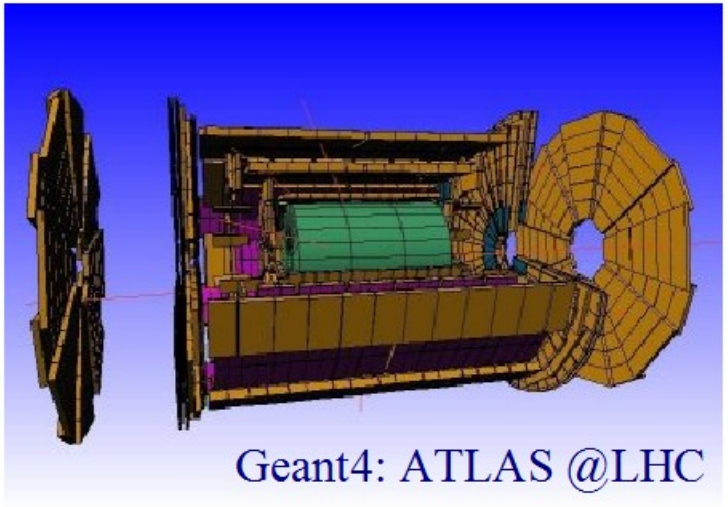


Collaborators also from non-member institutions, including
Budker Inst. of Physics
IHEP Protvino
MEPHI Moscow
Pittsburg University

http://geant4.cern.ch/geant4/

Papers based on Geant4 published each year (ISI, 10.10.12)





Geant4: ATLAS @LHC

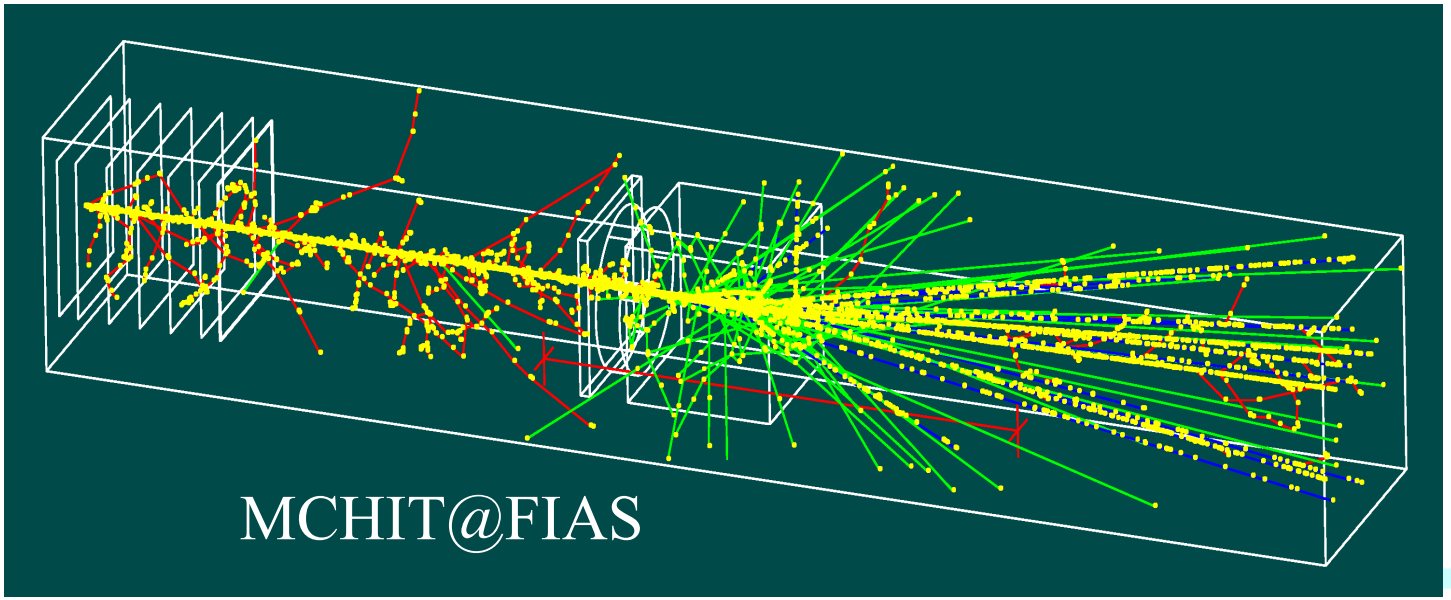
Geant4 toolkit

- Geant4 (for GEometry ANd Tracking) is a platform for the simulation of the propagation and interactions of particles in the matter.
- Developed and maintained by the international Geant4 Collaboration with headquarters at CERN (Geneva).
- The source code (in C++) is freely available.
- It provides an abundant set of physical models to handle diverse interactions of particles with matter over a wide energy range.
- It includes a complete set of tools for handling geometry, tracking, detector response, visualization and user interface.
- The user should build his own application using the relevant components of the toolkit.

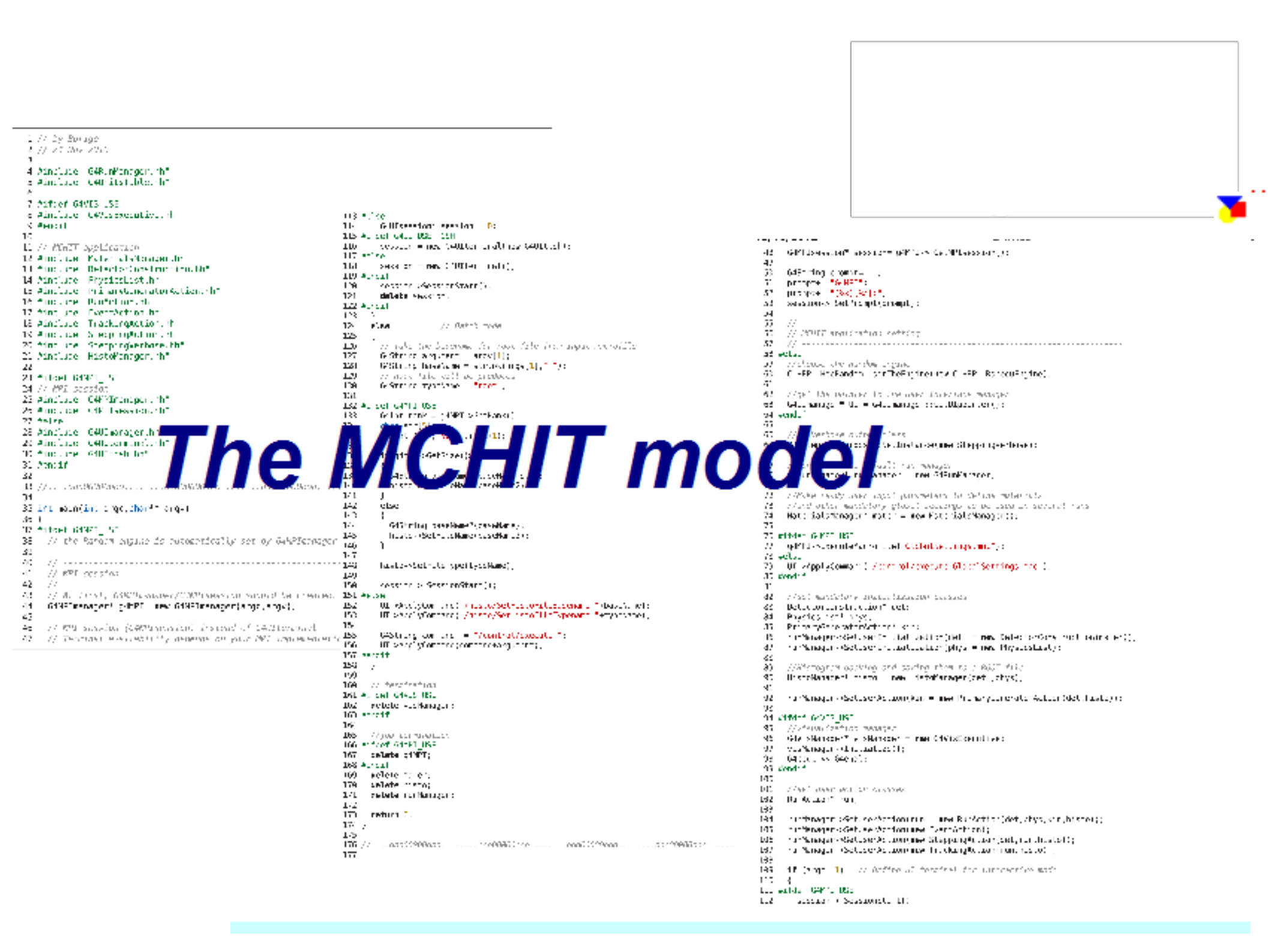
Agostinelli S et al. 2003 GEANT4—a simulation toolkit, Nucl. Instrum. Methods A 506 (2003) 250–303; has more than 7000 citations in Google database!

Monte Carlo for Heavy Ion Therapy (MCHIT) GEANT4-based application created at FIAS

- Uses FIAS expertise in heavy-ion physics (QMD and SMM);
- GEANT4 toolkit accumulates rich experience of international nuclear community over decades;
- GEANT4-based models are used now for modeling a rich verity of physical processes relevant to ion-beam therapy;
- Works with simple phantoms and beam-line elements;
- Simulations are done on event-by-event basis.



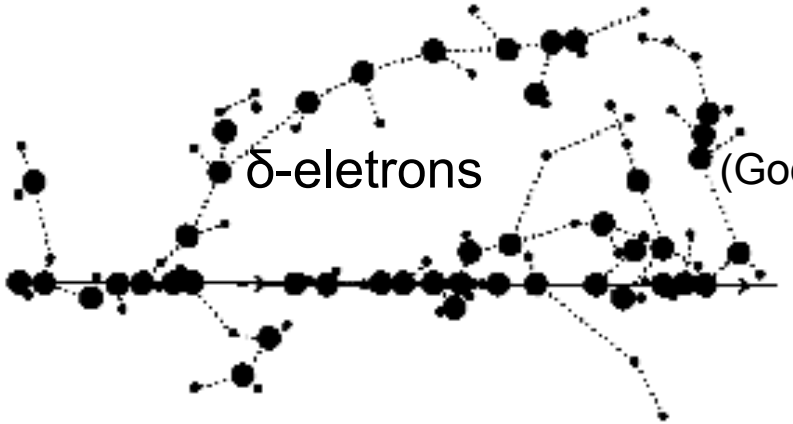
The MCHIT model



2. Models included in MCHIT

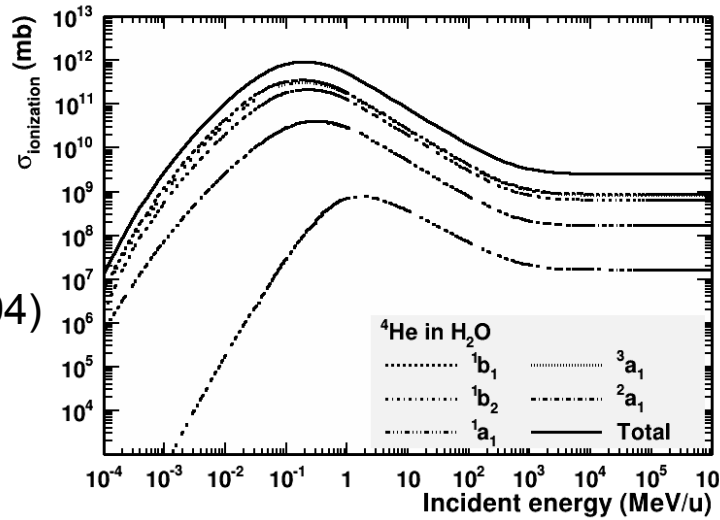
Relevant physical interactions in ion-beam cancer therapy

1. Coulomb scattering and ionizations arethe most frequent interaction processes for ions along their way to the tumour. described bv Bethe-Bloch formula

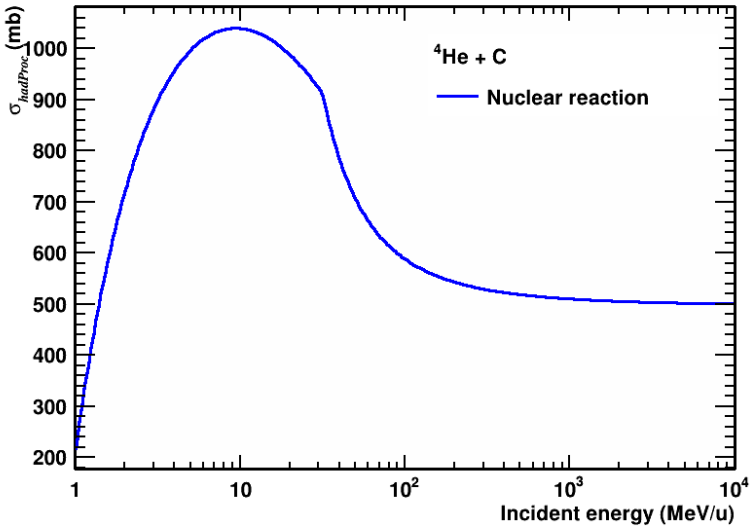


(Goodhead 1994)

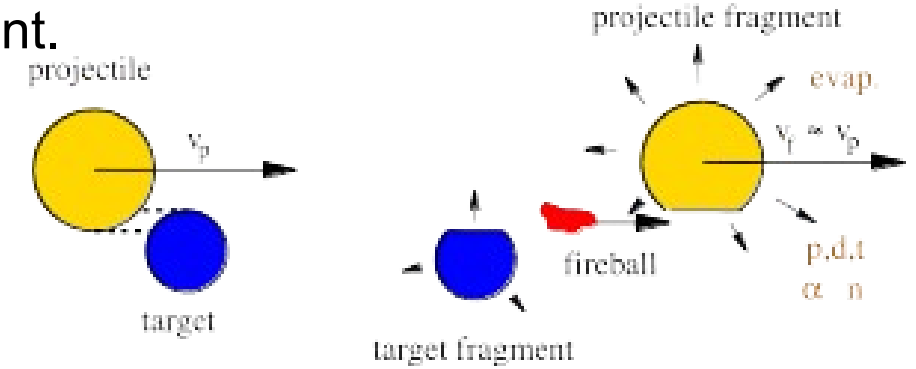
Ionization cross section



Nuclear reaction cross section

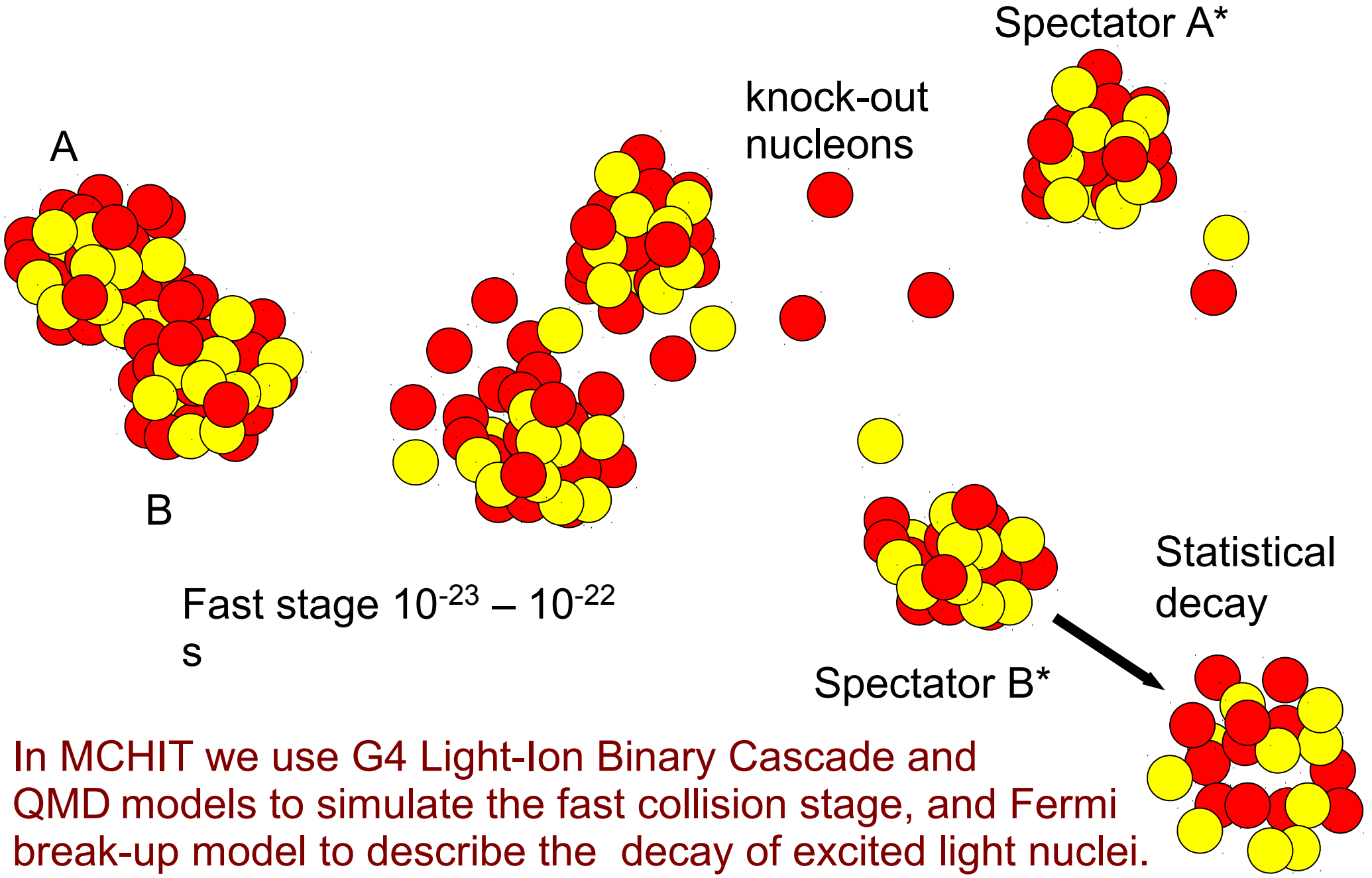


2. Nuclear collisions attenuate the beam particles and create secondary nuclei inside the patient.



(D. Schardt et al 2010)

Artist's view of a nucleus-nucleus collision



In MCHIT we use G4 Light-Ion Binary Cascade and QMD models to simulate the fast collision stage, and Fermi break-up model to describe the decay of excited light nuclei.

Our simulations are mostly done with:

- **Intra-Nuclear Cascade (INC liege) model:**
  - considers nucleus-nucleus collisions as a set of individual nucleon-nucleon collisions in the participant zone
  - estimates the excitation energy of residual nuclei as the sum of energies of holes (knocked-out nucleons) and particles (trapped nucleons)
  - Pauli-blocking is applied to NN collisions leading to occupied levels
  - local density approximation and scalar potentials for nucleons

- **Quantum Molecular Dynamics (QMD) model:**
  - each nucleon is represented as a Gaussian wave packet.
  - propagation with scattering term which takes into account Pauli principle
  - self-consistent potentials

Both models are combined to de-excitation codes of Geant4 to simulate further decays of hot (pre)fragments

De-excitation of residual nuclei

The **mass, charge and excitation energy** of excited residual nuclei are determined from the dynamical stage event-by-event.

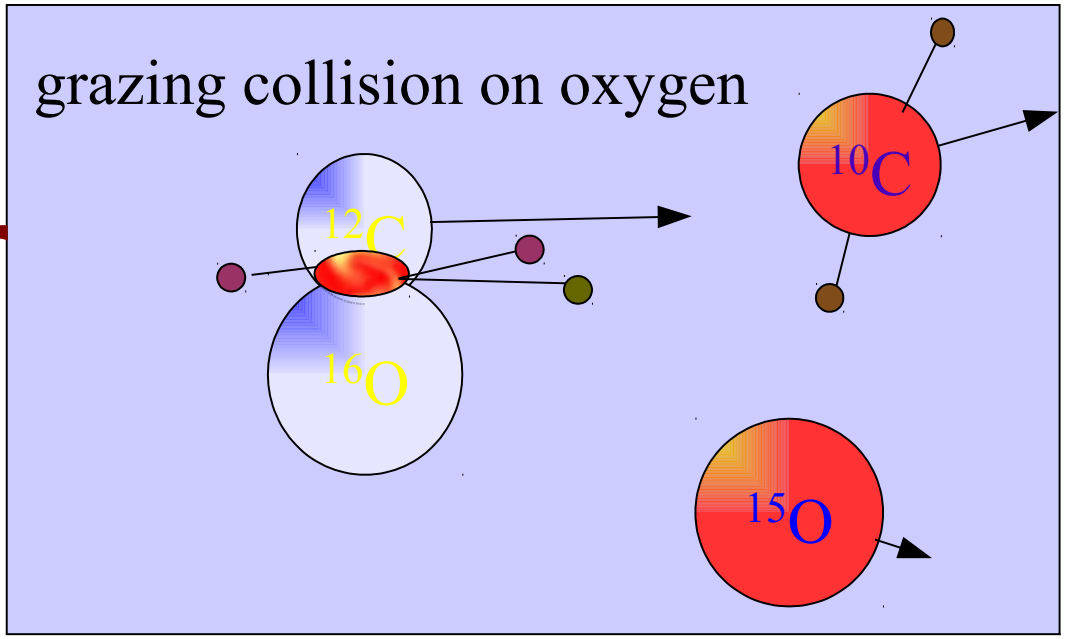
Decay channels for heavy residual nuclei are generated by Monte Carlo method, according to the **Evaporation Model** or **Statistical Multifragmentation Model (SMM)**.

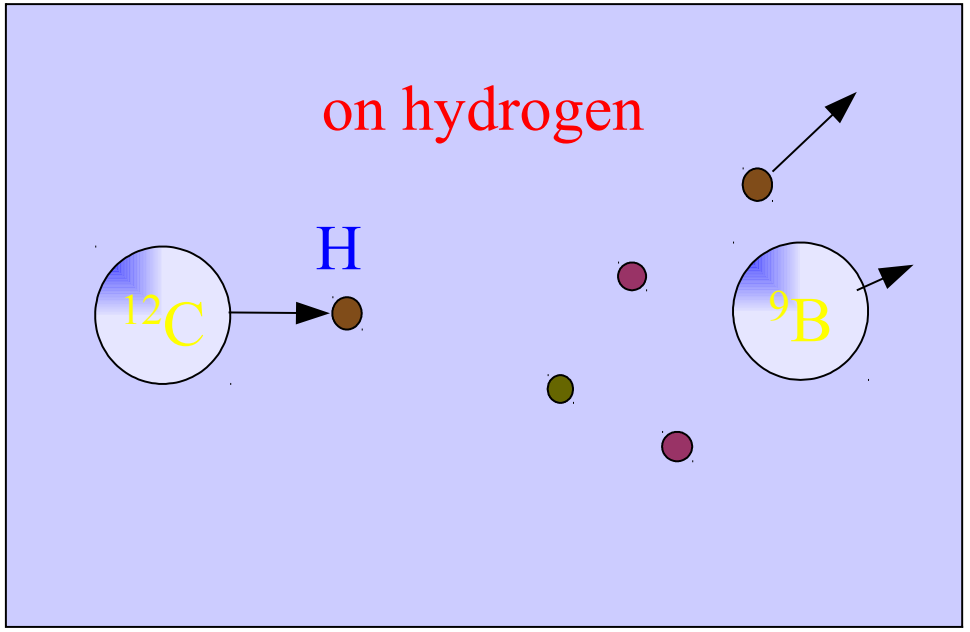
Fermi break-up model is used to simulate decays of highly excited ligh nuclei up to ^{16}O, all fragmentation channels are included
(this model works stable and has been validated before)

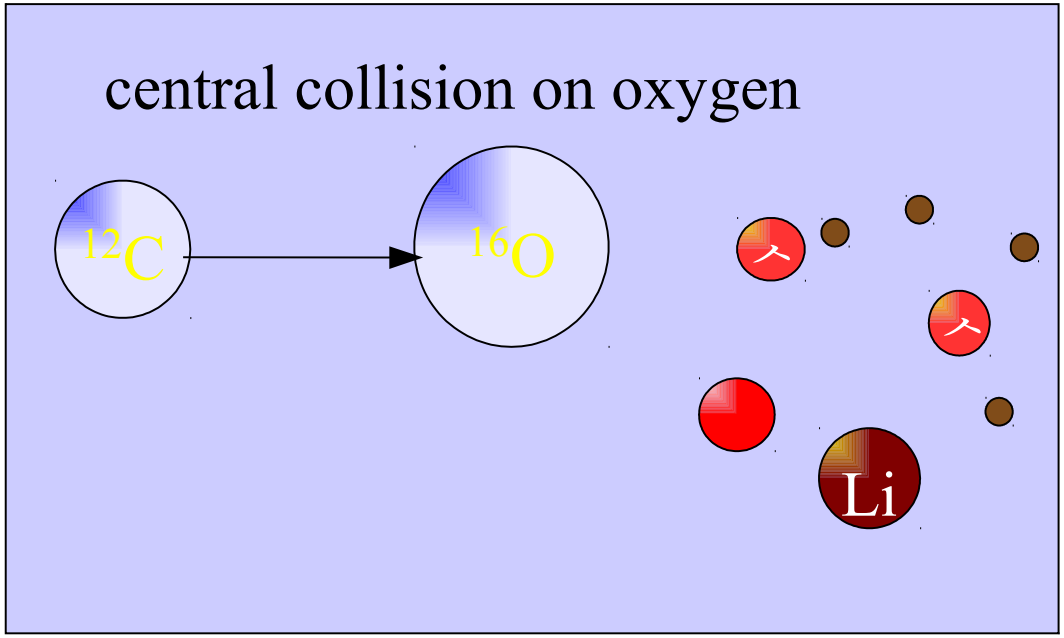
These models are verified by numerous experiments. They are used in nuclear physics community for decades

3. MCHIT-based simulations of ion-beam therapy

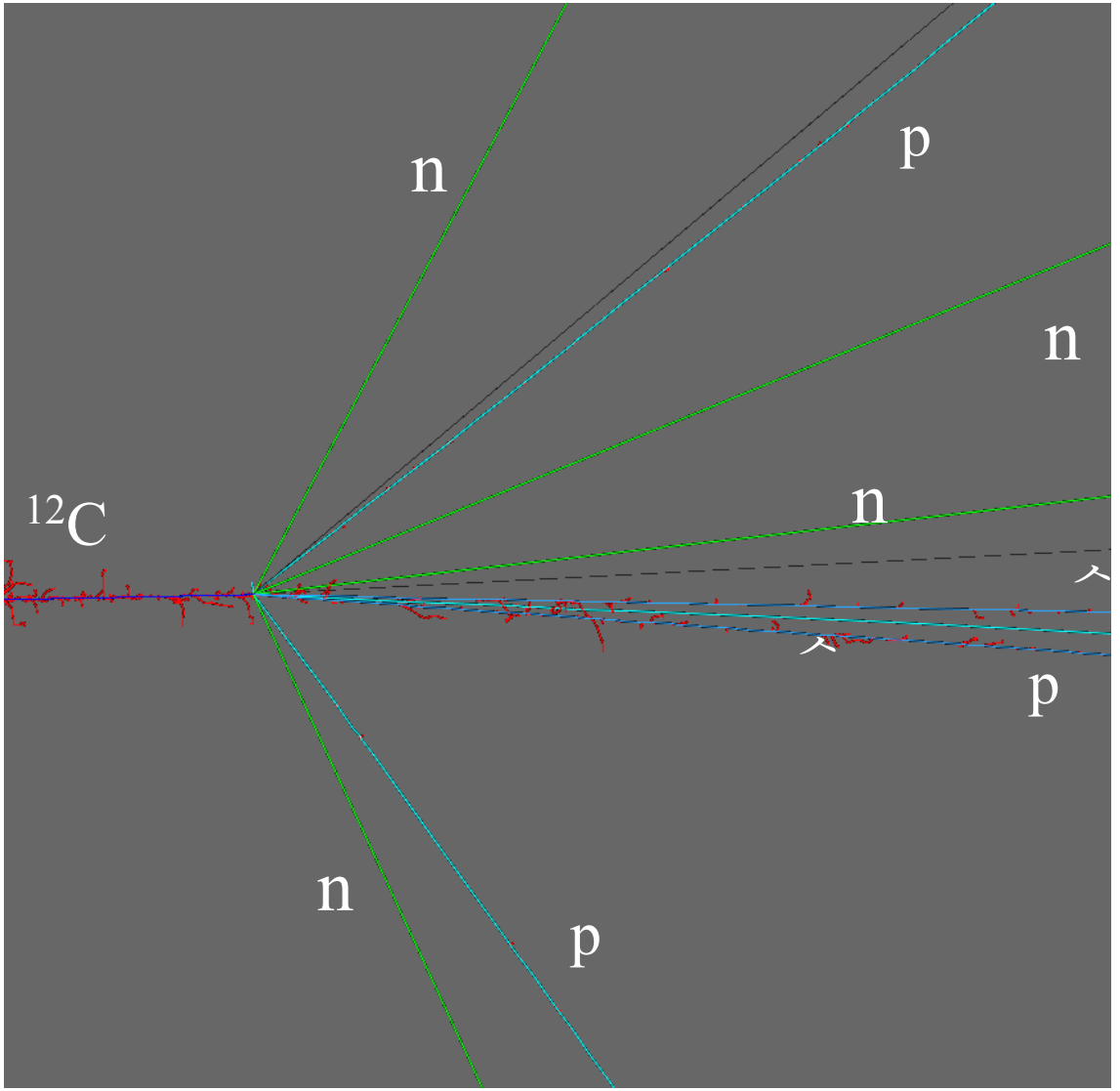
^{12}C break-up processes in water simulated with MCHIT





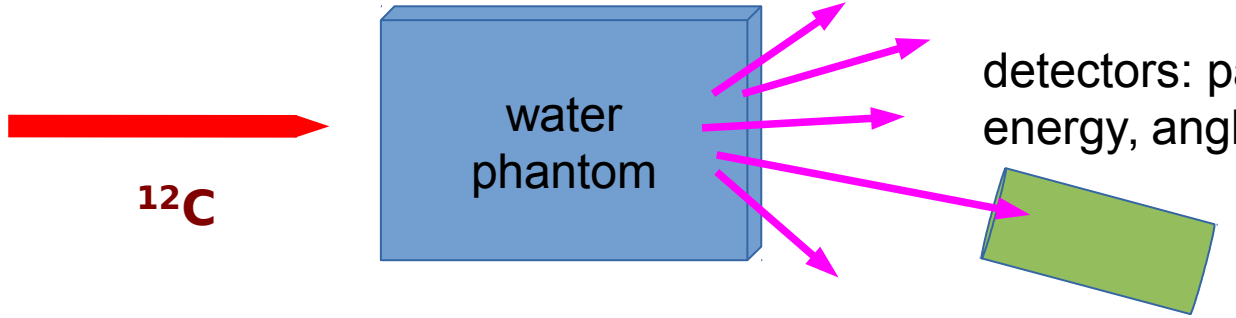


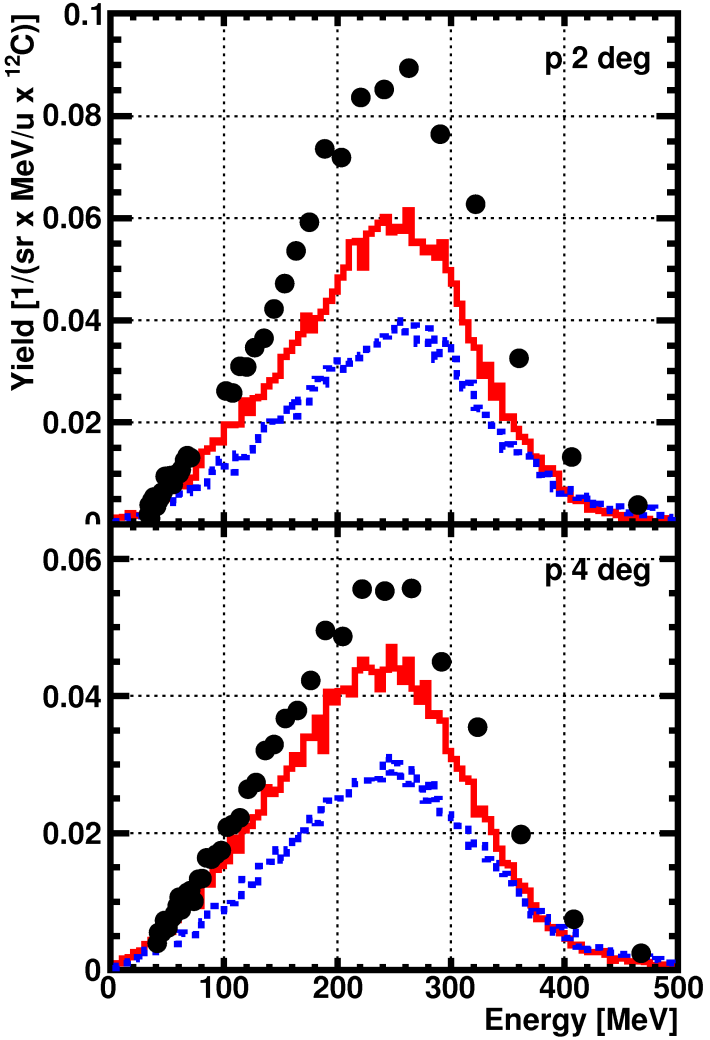
One ^{12}C break-up event simulated with MCHIT on macro scale

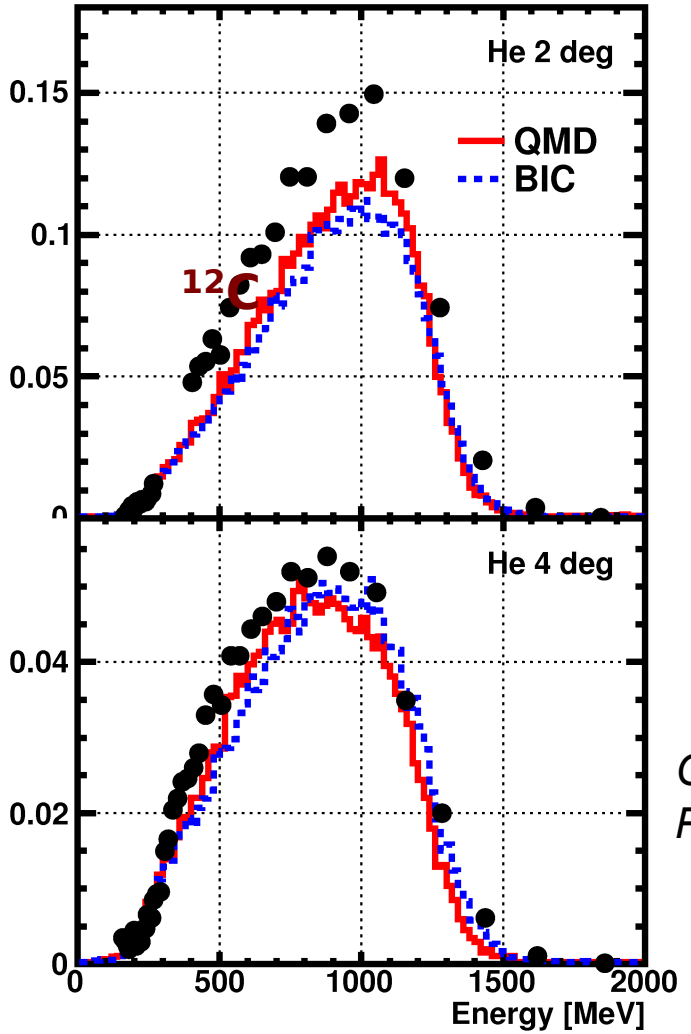


Models at work, BIC vs QMD: energy spectra

GSI experiment:





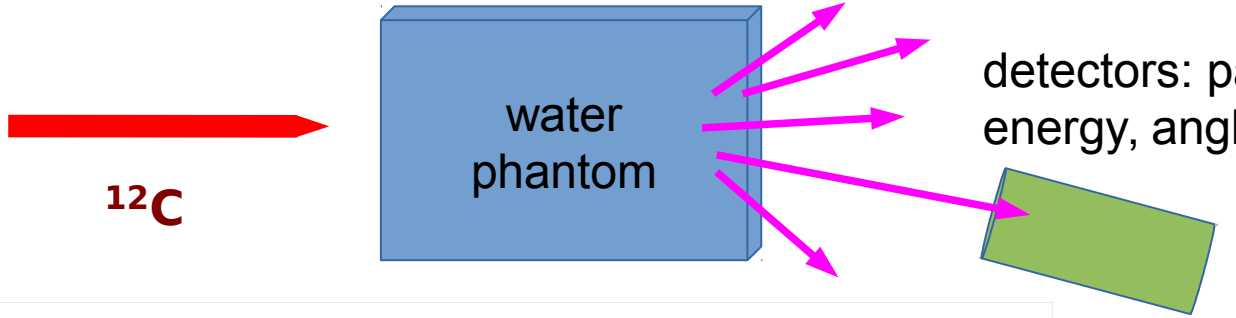


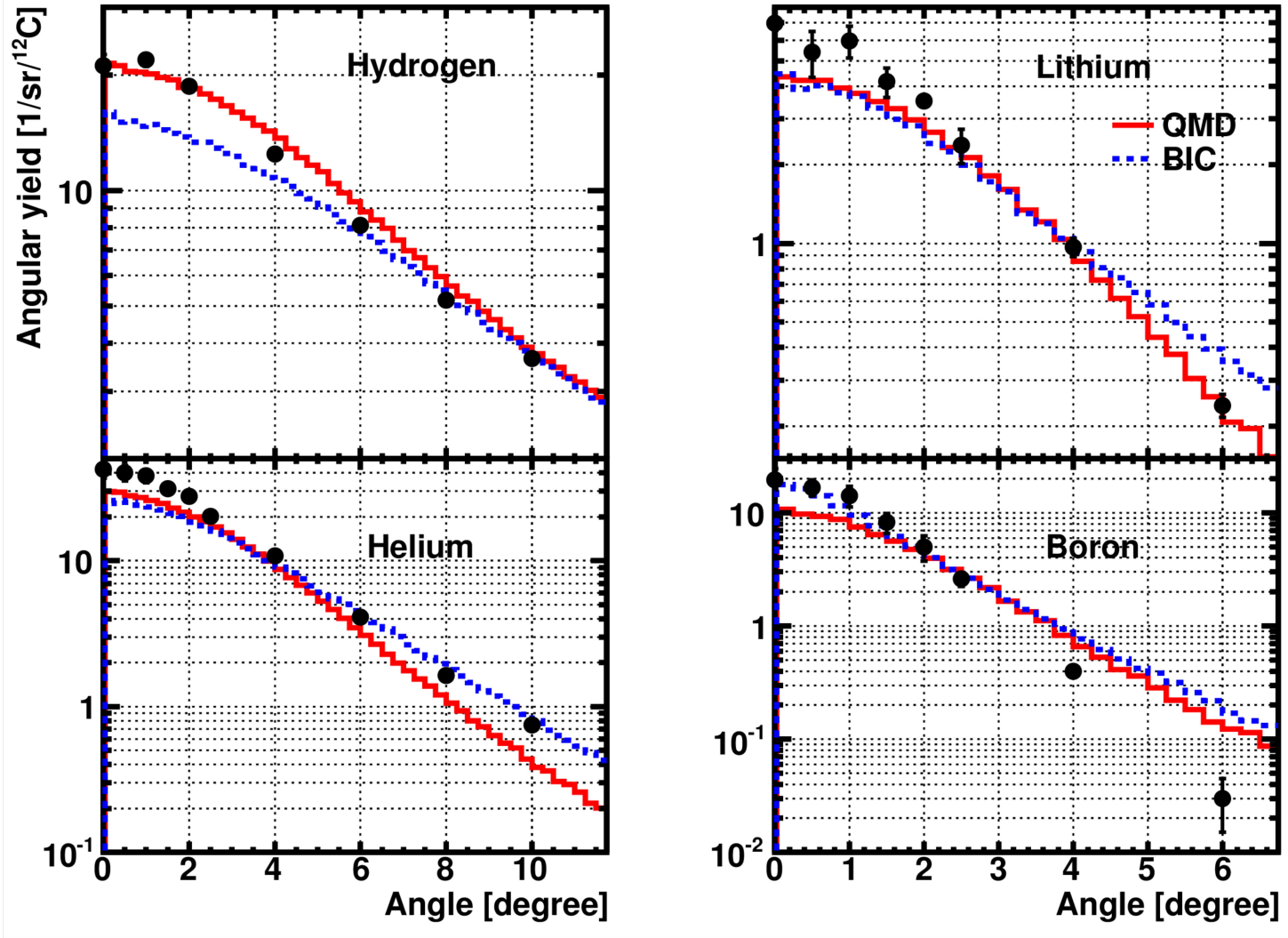
QMD is closer to data, but still not perfect Max. deviations on level of 30%

GSI Data: E. Haetner et al., PMB 58, 8265 (2013)

Models at work, BIC vs QMD: angular distributions

GSI experiment:





QMD is better compared to BIC

GSI data: E. Haetner et al.,
PMB 58, 8265 (2013)

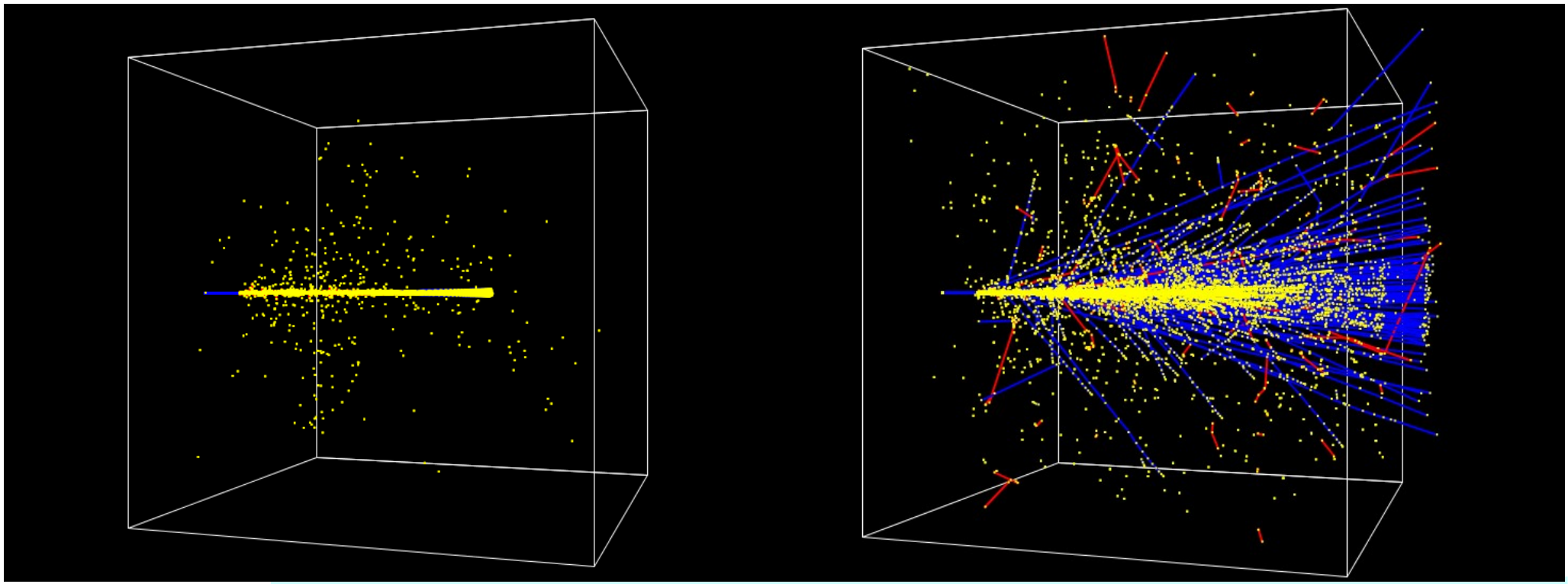
Importance of nuclear fragmentation reactions in carbon therapy

100 events of ^{12}C @ 330 AMeV in water cube $(30\ cm)^3$

fragments and protons in blue, electrons in red, yellow dots are interaction points

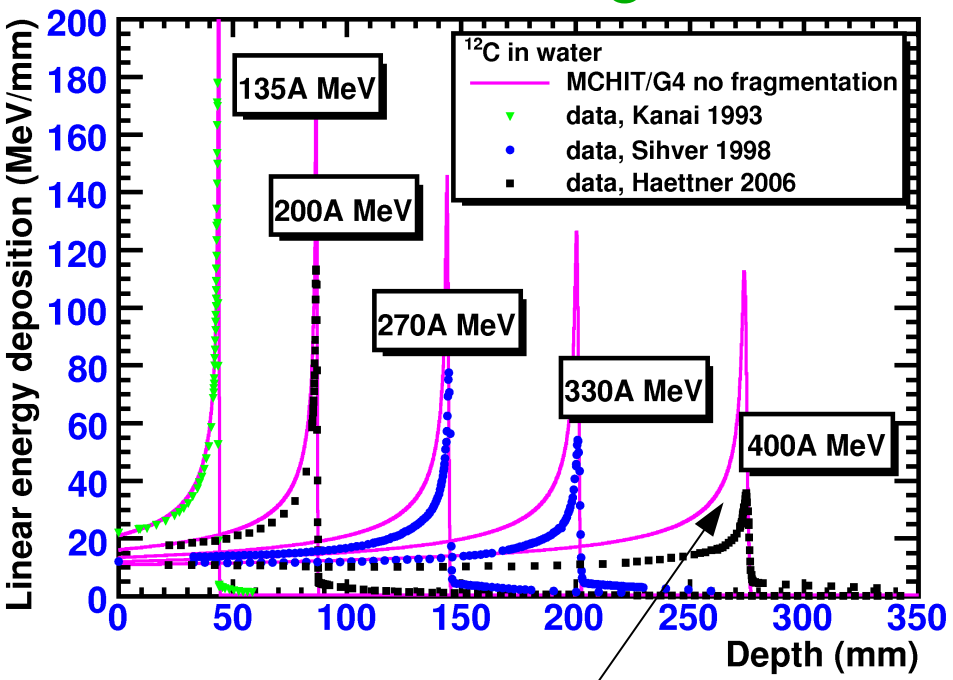
Electromagnetic interactions only

EM interactions + hadronic elastic scattering and fragmentation reactions



Precise dose calculations have to account for fragmentation reactions, otherwise...

without nuclear fragmentation

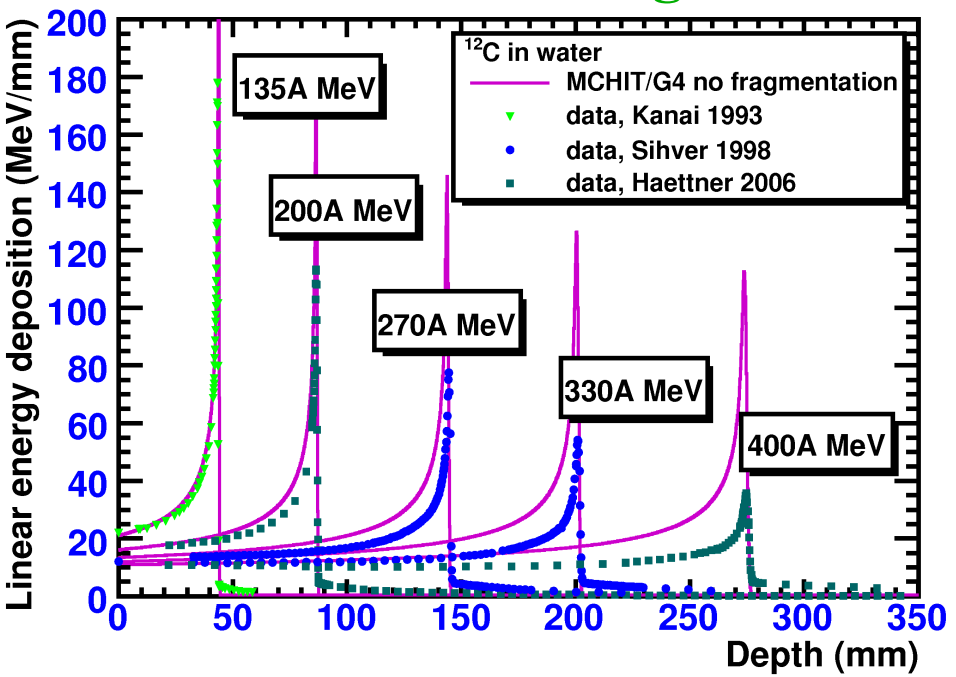


the dose would be largely overestimated at deep penetrations. The fragmentation of nuclei leads to the reduction of energy deposition on the way to the Bragg peak

$$Z^2=(Z_1+Z_2+...)^2>Z_1^2+Z_2^2+...$$

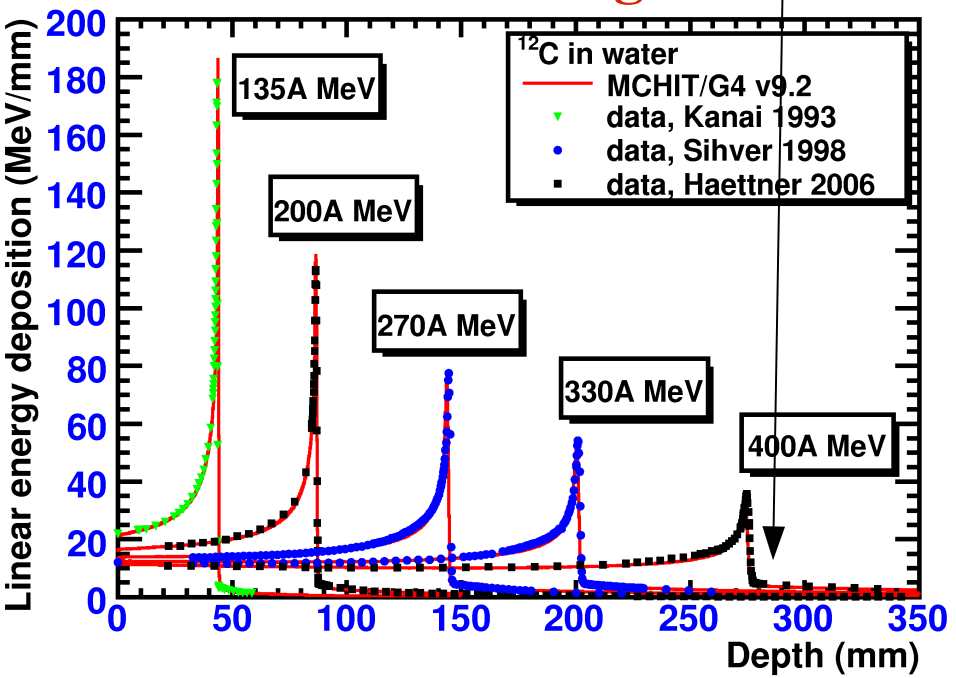
Precise dose calculations must account for fragmentation reactions!

without nuclear fragmentation



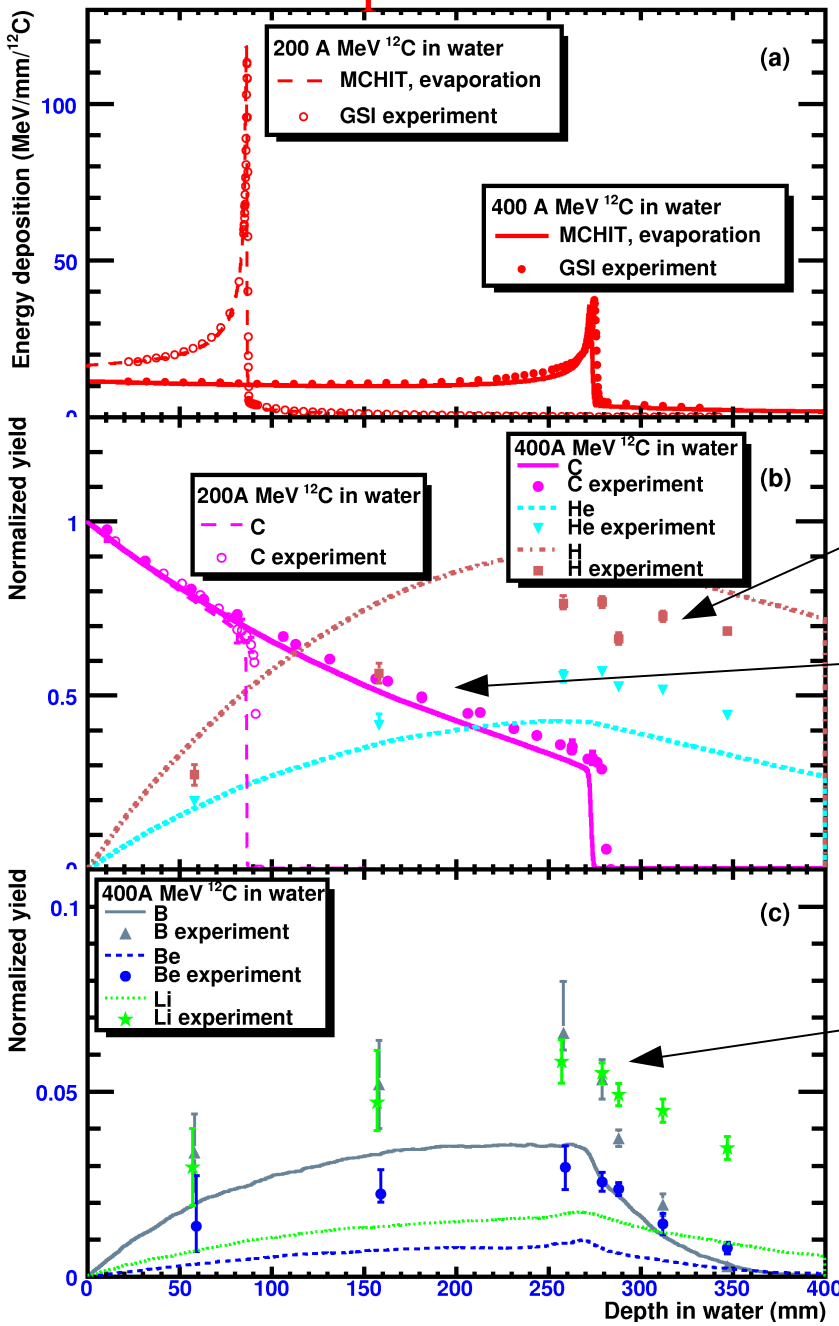
Dose tails beyond the Bragg peak, produced by the light secondary fragments (n, p, He,...), should be accurately accounted for in the treatment planning (~10% effect!).

with nuclear fragmentation



Secondary fragments: models work

Evaporation



Calculations with the Wilson abrasion model: Bragg peaks well reproduced

Yields of protons are overestimated

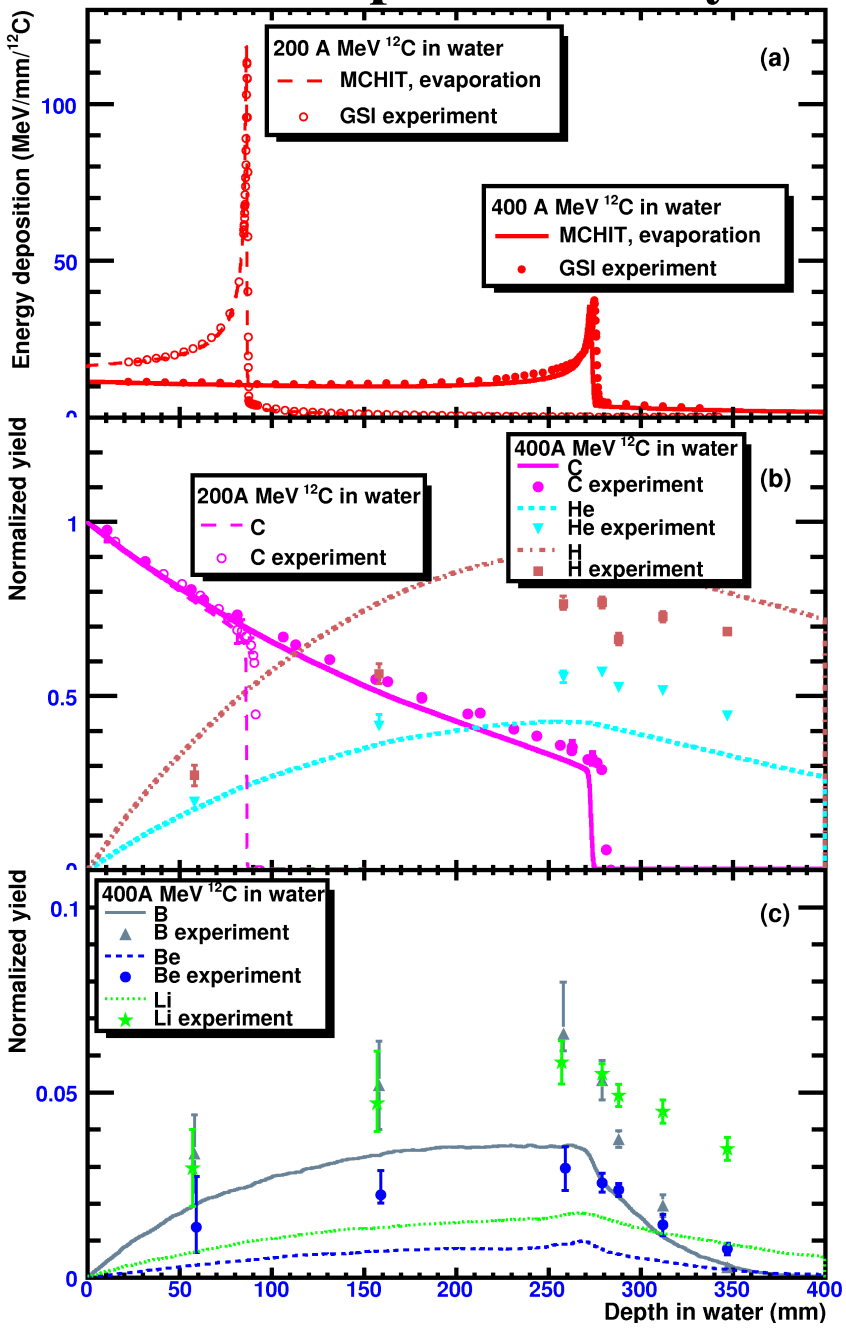
30 to 70% of beam ions are destroyed in nuclear fragmentation reactions

Yields of Li, Be and B are too low

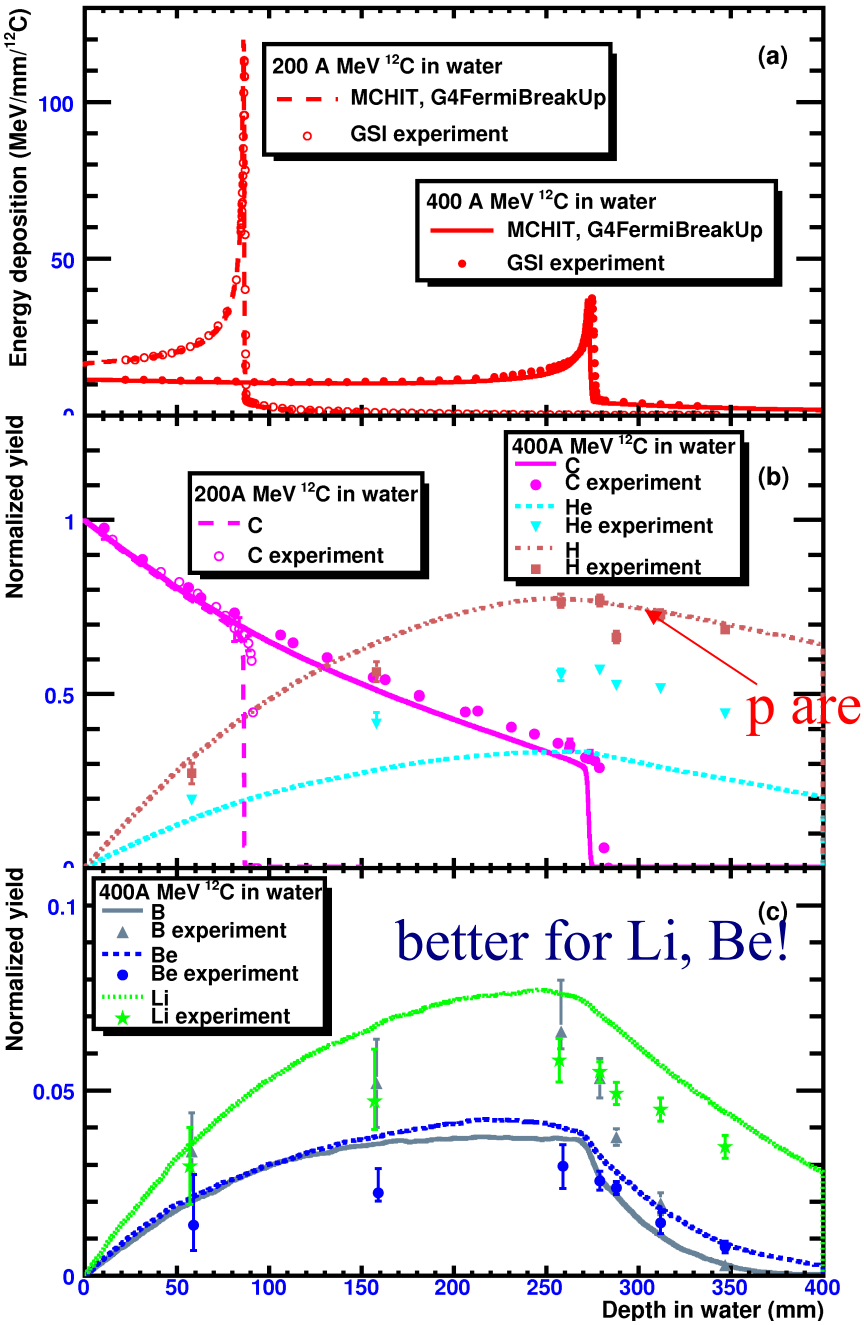
data: *E. Haettner et al., Rad. Prot. Dosim. 122 (2006)48*, within θ_x, θ_y <10° acceptance

Secondary fragments: models at work

Evaporation only

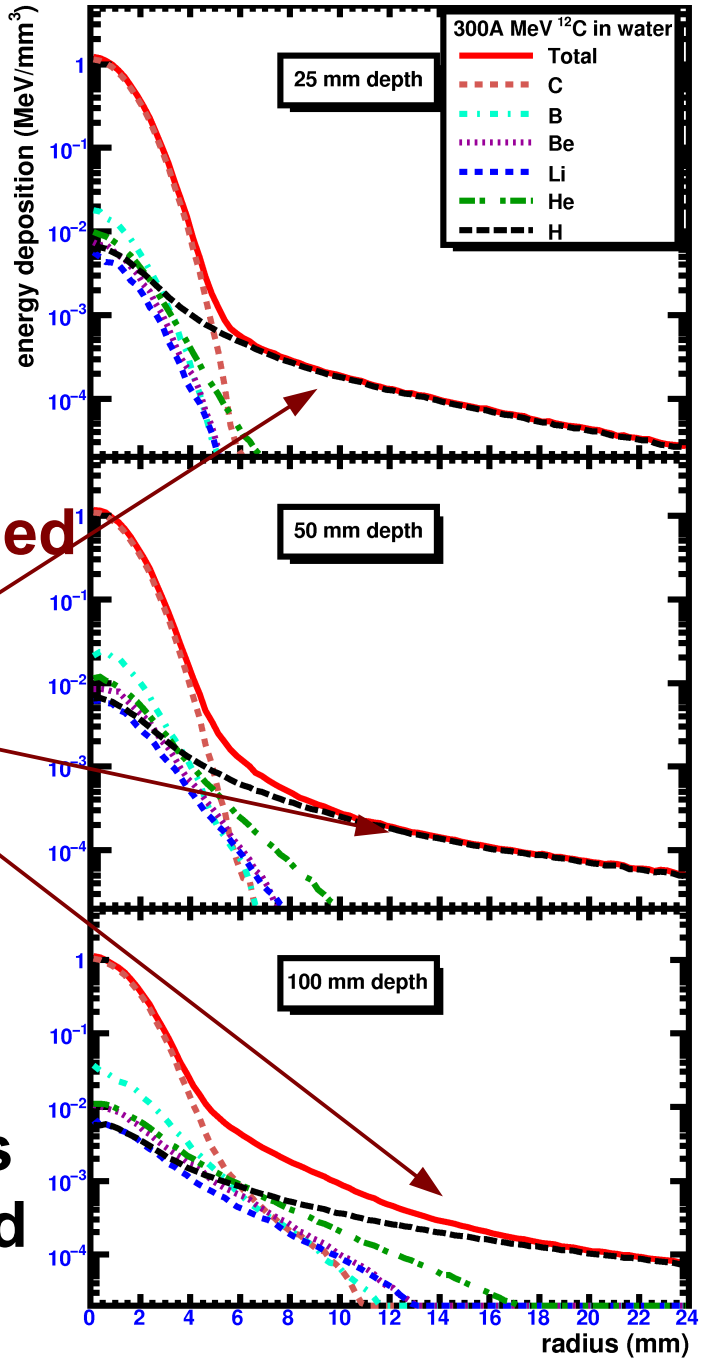


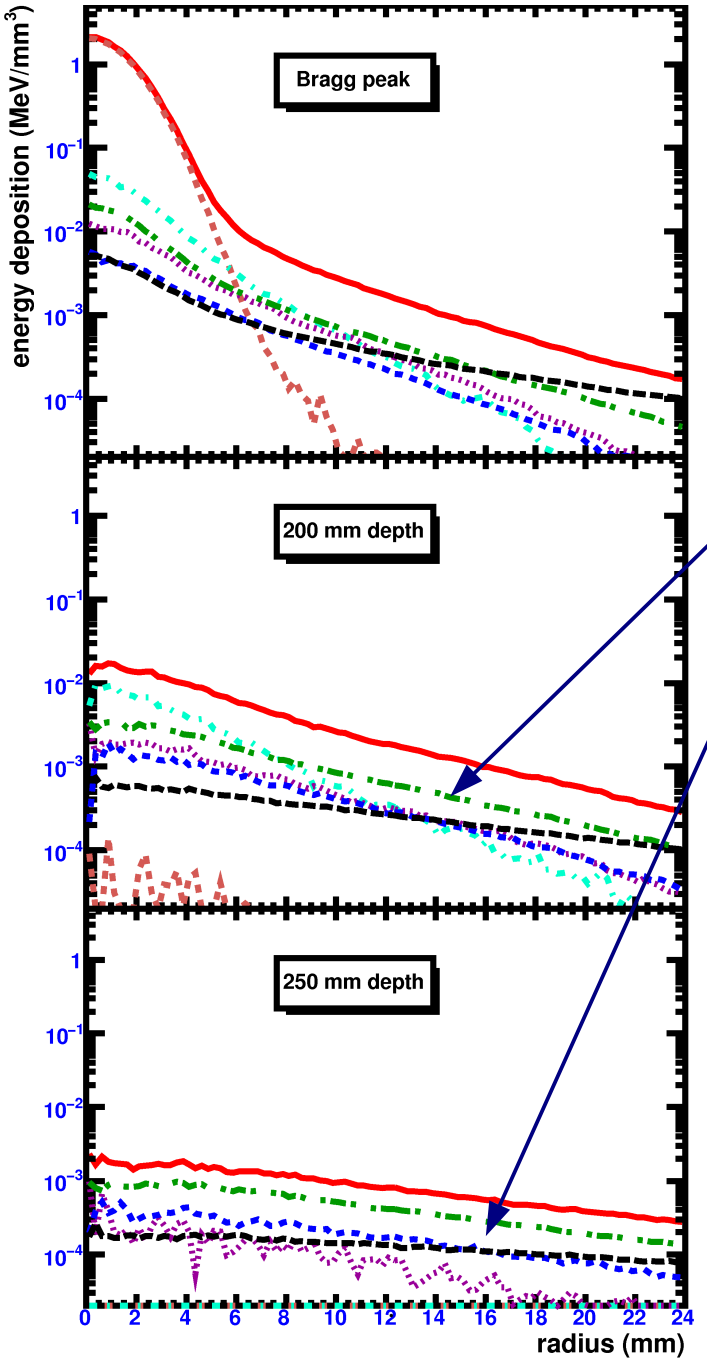
Fermi break-up added



data: *E. Haettner et al., Rad. Prot. Dosim. 122 (2006)48*, within θ<10o acceptance

Radial distributions of dose for different depths



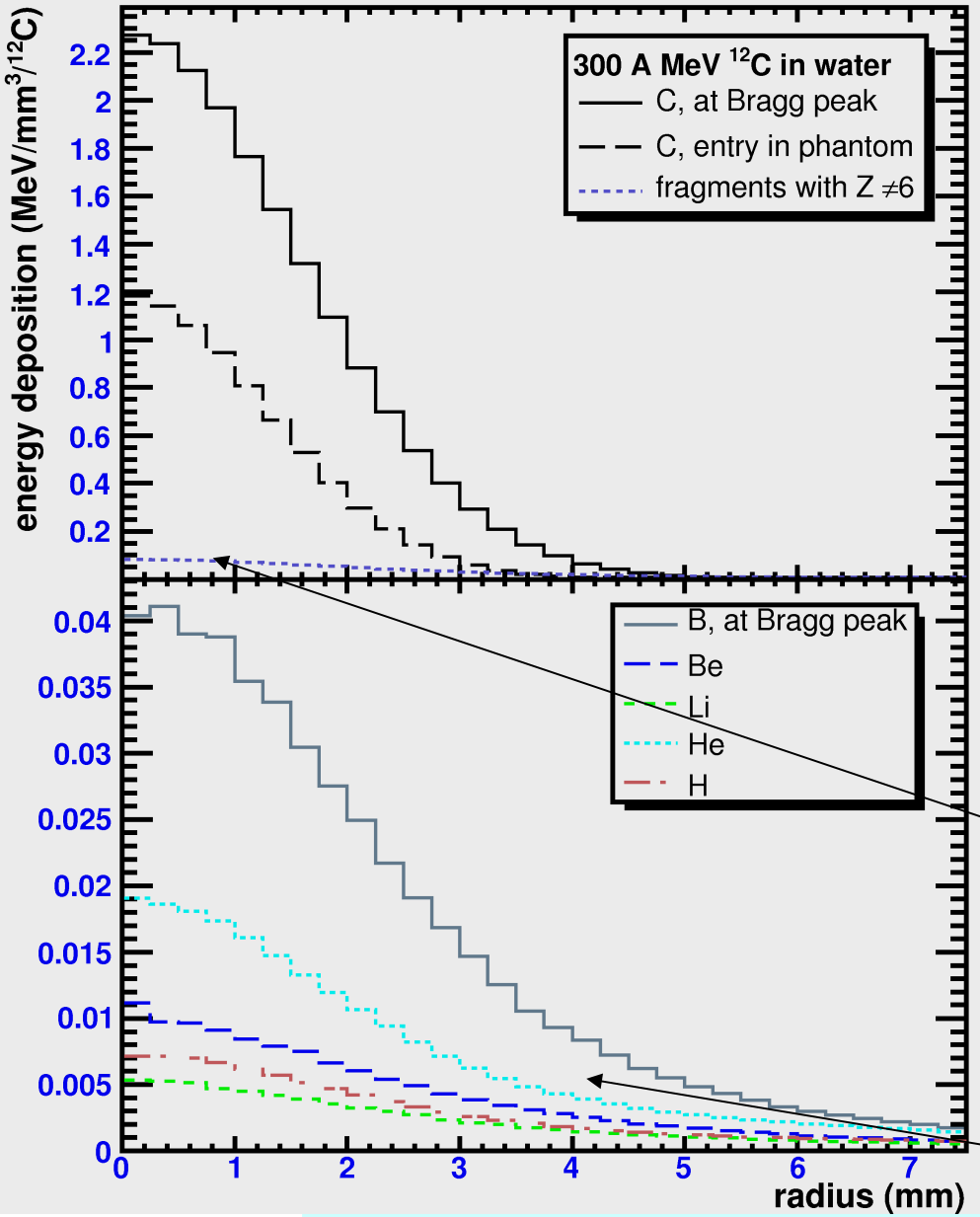


^{12}C beam is surrounded by protons

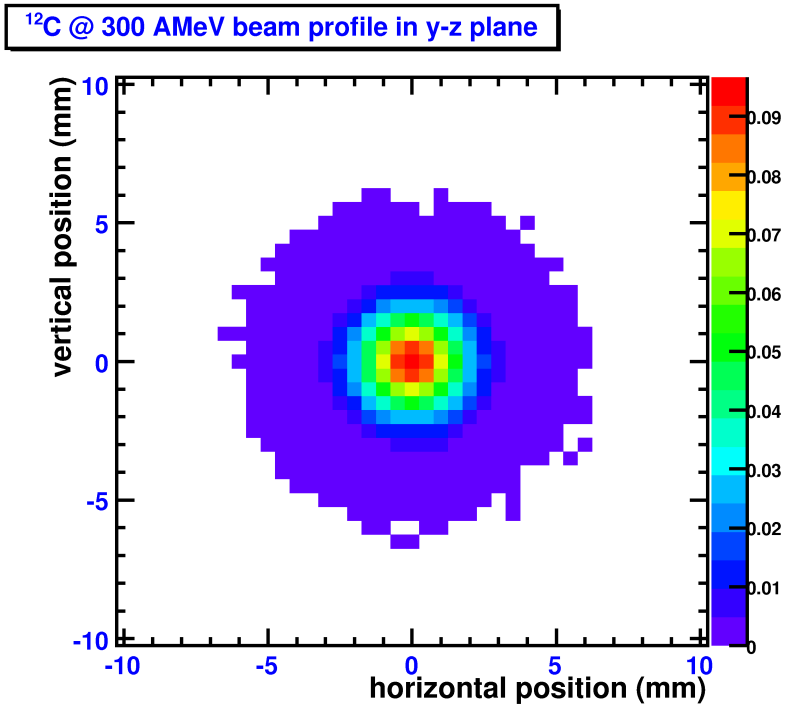
Recoil protons created in neutron interactions are included

Mostly He fragments after the peak

Radial distributions of secondary fragments

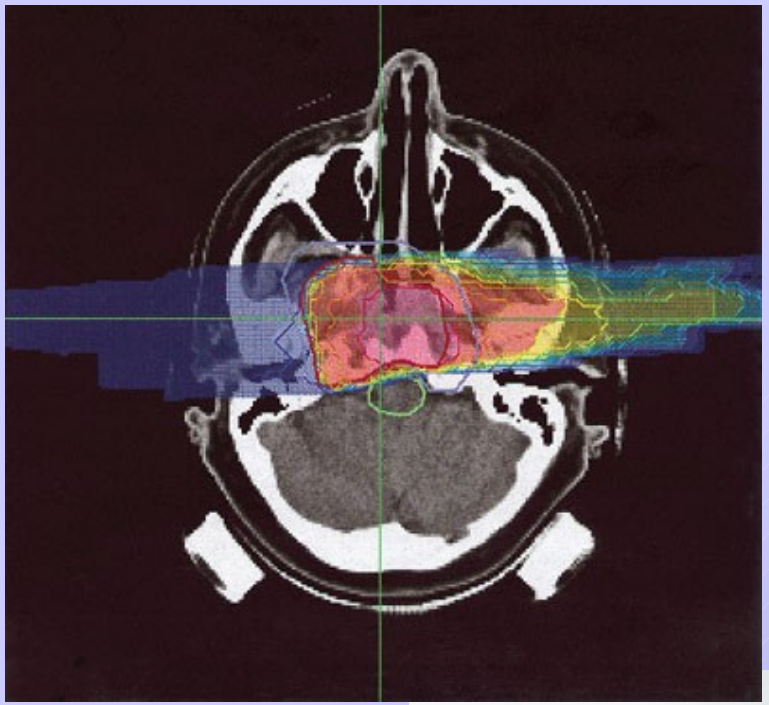


300 A MeV 12C beam with 3 mm FWHM



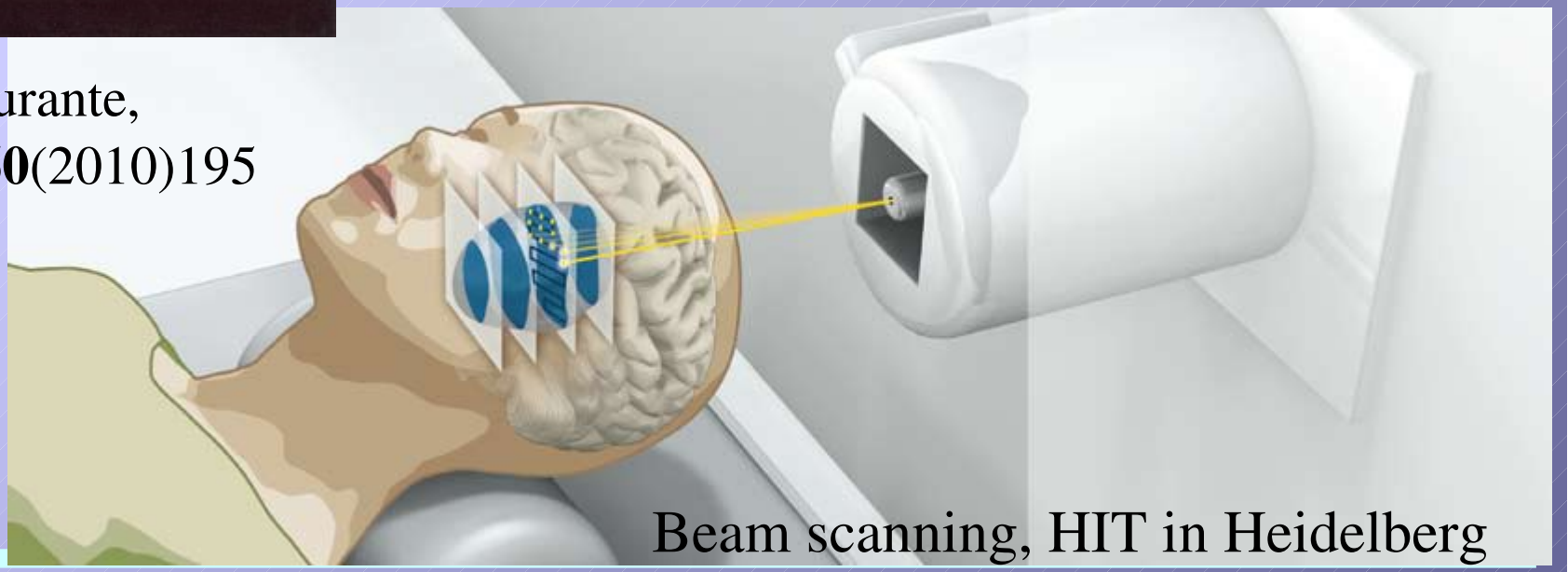
Contribution from secondary fragments is small at the beam axis, but is very essential at the periphery!

Thorough treatment planning and precise dose delivery are crucial for success



- **Full 3D and 4D (with accounting for organ movement during irradiation) treatment planning**
- **Thin (pencil-like, ~ 3 mm FWHM) beams**
- **Active beam scanning technique: fast variation of beam energy and direction**
- **Optimization of biological dose in tumor**

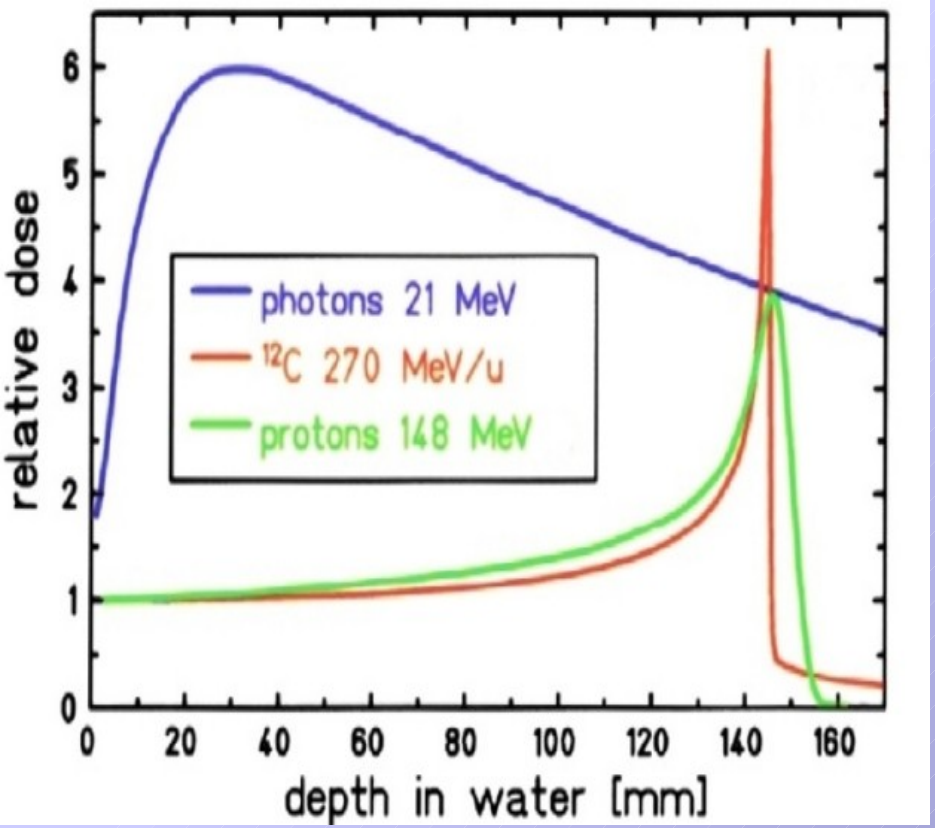
M.Krämer, M.Durante,
Eur. Phys. J. D **60**(2010)195



Beam scanning, HIT in Heidelberg

2. Basic concepts of radiobiology

Advantages of ions compared to photons



Source: Kraft *Prog. Part. Nucl. Phys.* **45** (2000)

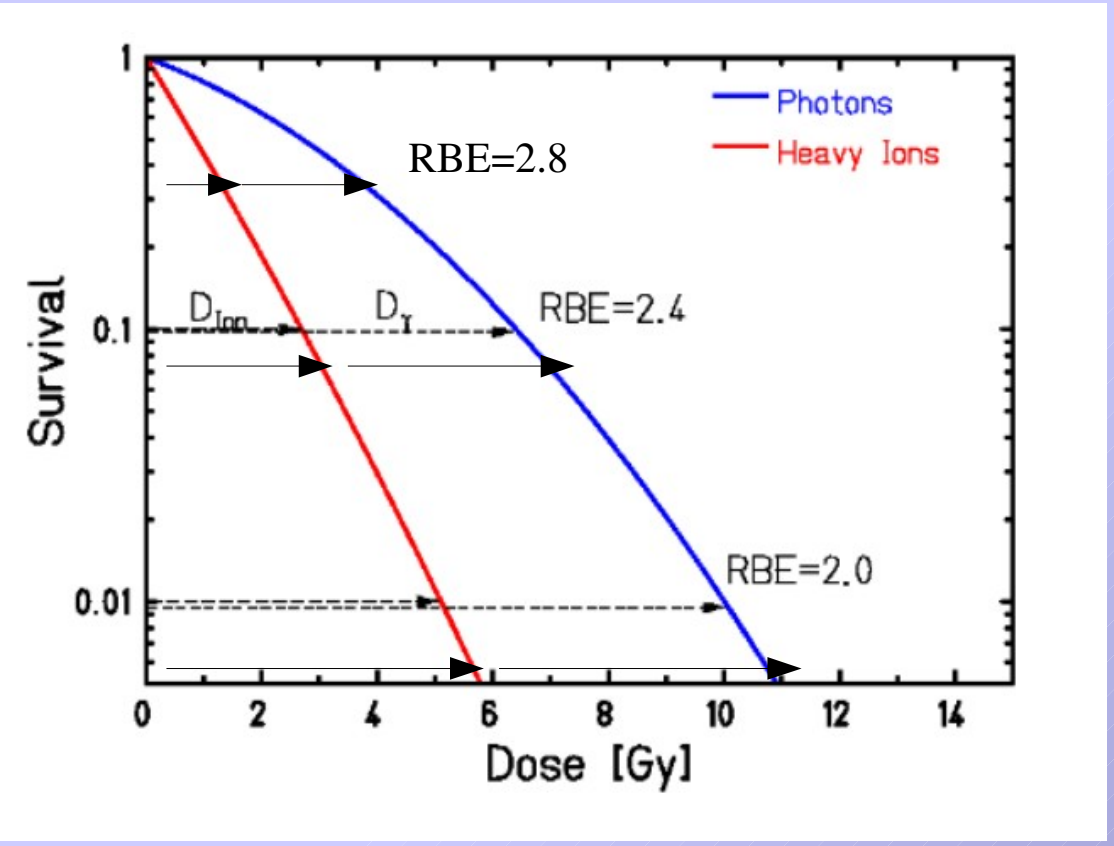
Energy deposition of ions:

- inverse depth-dose profile called Bragg peak
- depth of the peak can be changed with the kinetic energy of the incident ions

Energy deposition of photons

- exponential decrease of energy deposition with depth
- uncorrelated ionization events

Relative Biological Effectiveness (RBE)



Source: Kraft *Prog. Part. Nucl. Phys.* **45** (2000)

- **Dose D is energy deposited in unit mass**

$$D=\frac{dE}{dm} \quad \text{Unit} \quad 1Gy=1\frac{J}{kg}$$

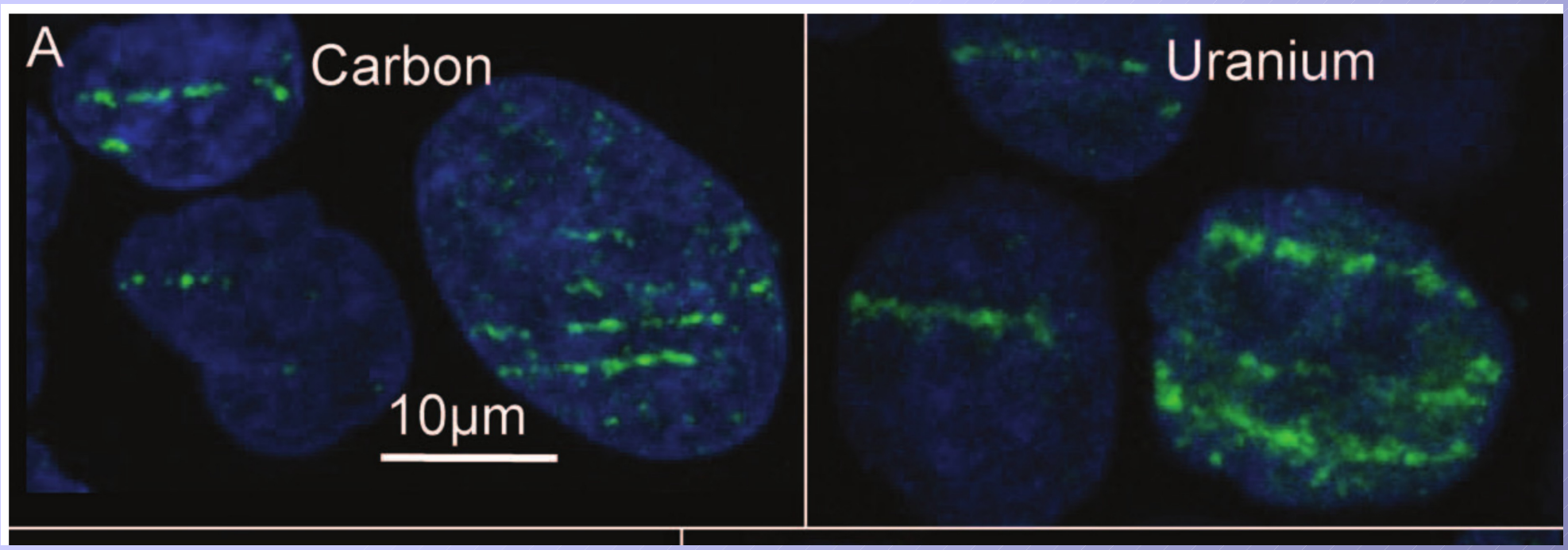
- **Ions show increased effectiveness compared to photons**
- **At given survival fraction**

$$RBE=\frac{D_X}{D_I}$$

- **Biological dose =** $RBE \cdot D_I$

- **Linear-Quadratic model:** $S=exp(-\alpha D-\beta D^2)$ **, where parameters depend on the cell kind and type of radiation**
- **Ions like 12C have RBE up to 2-3**

Ion tracks inside cell nuclei: visualization of damage sites by fluorescent proteins



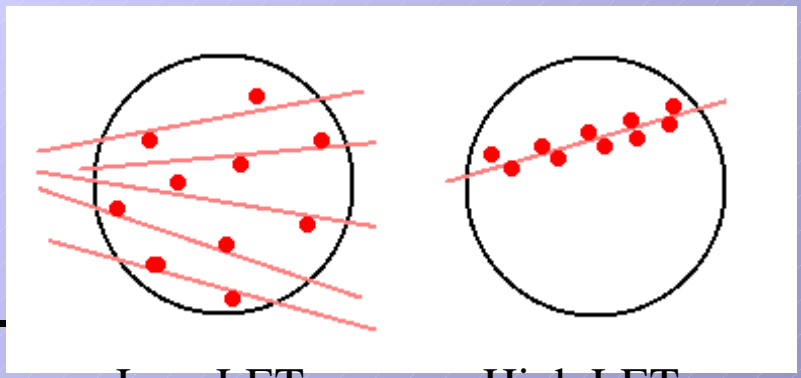
^{12}C 9.5A MeV and ^{238}U 3A MeV as seen by in-beam microscopy. Proteins 53BP1 and RPA (green) are related to DNA repair processes after the damage induced by ions traversing cell nuclei. *(B. Jakob et al. 2009, Rad. Res. 171 405).*

Energy imparted to a cell nucleus per unit track length is an important characteristic which defines the respective biological effects.

DNA breaking mechanisms

Photons D_x = Heavy ions D_{ion}

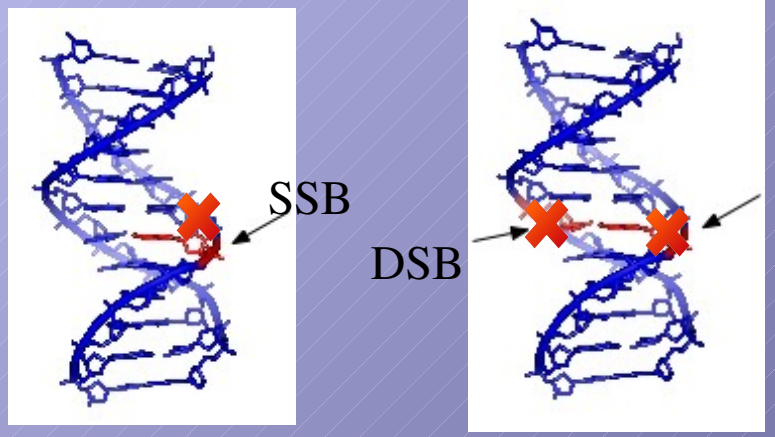
- Cell nucleus is its most sensitive structure. It contains the DNA, double-helix molecule, which is responsible for the genetic code



Low LET High LET

- Breaking one of the two strands can be repaired - **Single Strand Break (SSB)**

- Breaking both strands can be hardly repaired - **Double Strand Break (DSB)**



Cell death

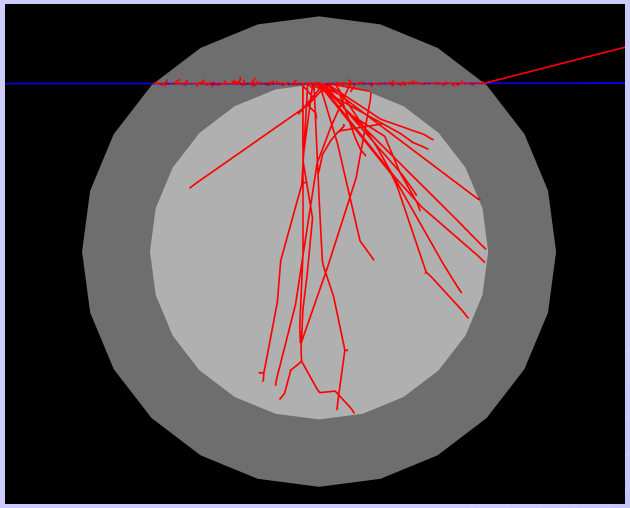
- RBE increases with increasing local ionization density until a point of saturation has been reached (LET~ 120 keV/μm)
- Cell repair and survival mechanisms are very strong, should be included in treatment planning

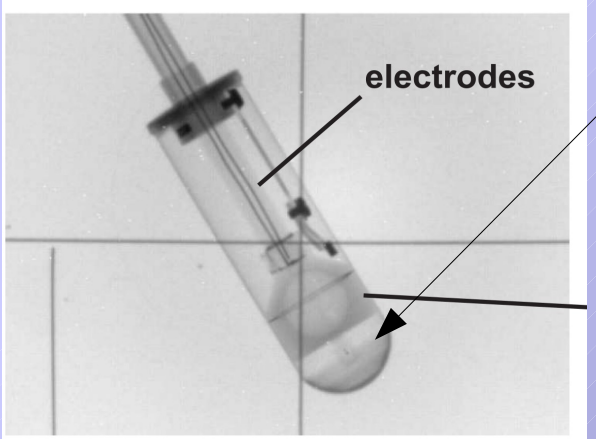
$Survival_x \gg Survival_i$

3. Microdosimetry

Tissue Equivalent Proportional Counter (TEPC)

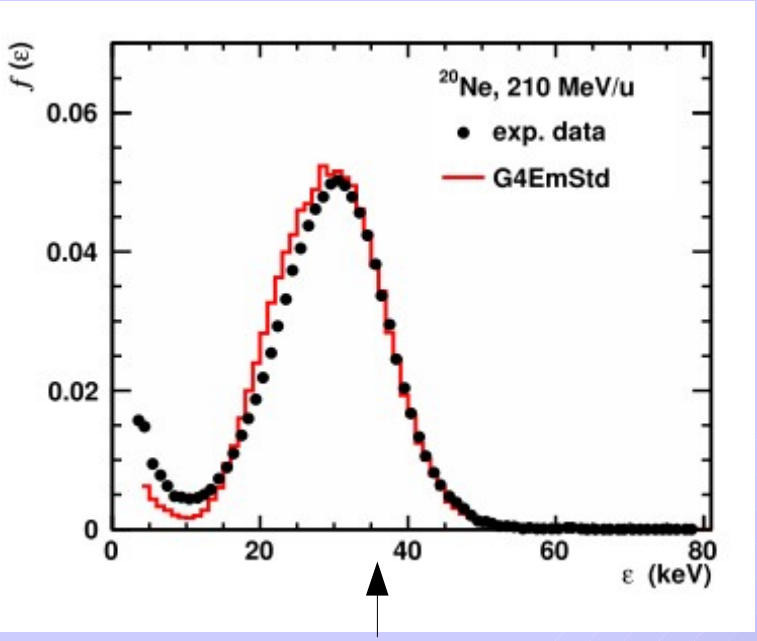
d ~ 12 mm





- Method proposed by Rossi at al. in 1950s.
- Local density of ionization can be measured by small ionization detectors - TEPC
- TEPC represents a region of micrometer size of tissue by a diluted gas, e. g. propane, in a bigger volume
- energy deposition to a cell nucleus (d~10 μm) can be measured event-by-event

Lineal energy distributions



y*

The total energy deposited in an individual TEPC is measured event-by-event

Imparted energy: $\varepsilon = \sum \varepsilon_i$

Lineal energy: $y = \varepsilon / \bar{l}$

Probability density $f(y)$

Frequency-mean lineal energy $\ddot{y} = \int_0^\infty y\, f(y)\, dy$

Relation to the macroscopic dose

$$D[Gy] = \frac{0.204}{d^2}\bar{y}_f$$

d – diameter of the sensitive volume, in μm, y_f – in keV/μm

Saturation-corrected dose-mean lineal energy

$$y^* = \frac{y_0^2 \int_0^\infty [1 - \exp(-y^2/y_0^2)] f(y)\, dy}{\int_0^\infty y f(y)\, dy}$$

Microdosimetric Kinetic Model (MKM)

The parameters of the LQ model for ions can be estimated using the Microdosimetric-Kinetic Model (MKM, Hawkins 2003, Kase et al. 2006):

$$\alpha = \alpha_0 + \frac{\beta y^\star}{\rho \pi r_d^2}$$

where α_0 and β are determined from the survival curve for X-rays (reference radiation), r_d = 0.42 μm is the radius of a sub-cellular domain in MKM, ρ = 1 g/cm^2. y^* is saturation corrected dose-mean lineal energy (ICRU, 1983) determined using microdosimetry spectra:

$$\mathrm{y}^* = \frac{y_0^2 \int_0^\infty \left(1 - \exp\left(-y^2/y_0^2\right)\right) f(y)\mathrm{d}y}{\int_0^\infty y f(y)\mathrm{d}y}$$

It is introduced to account for the saturation of biological effects induced by high-LET radiation.

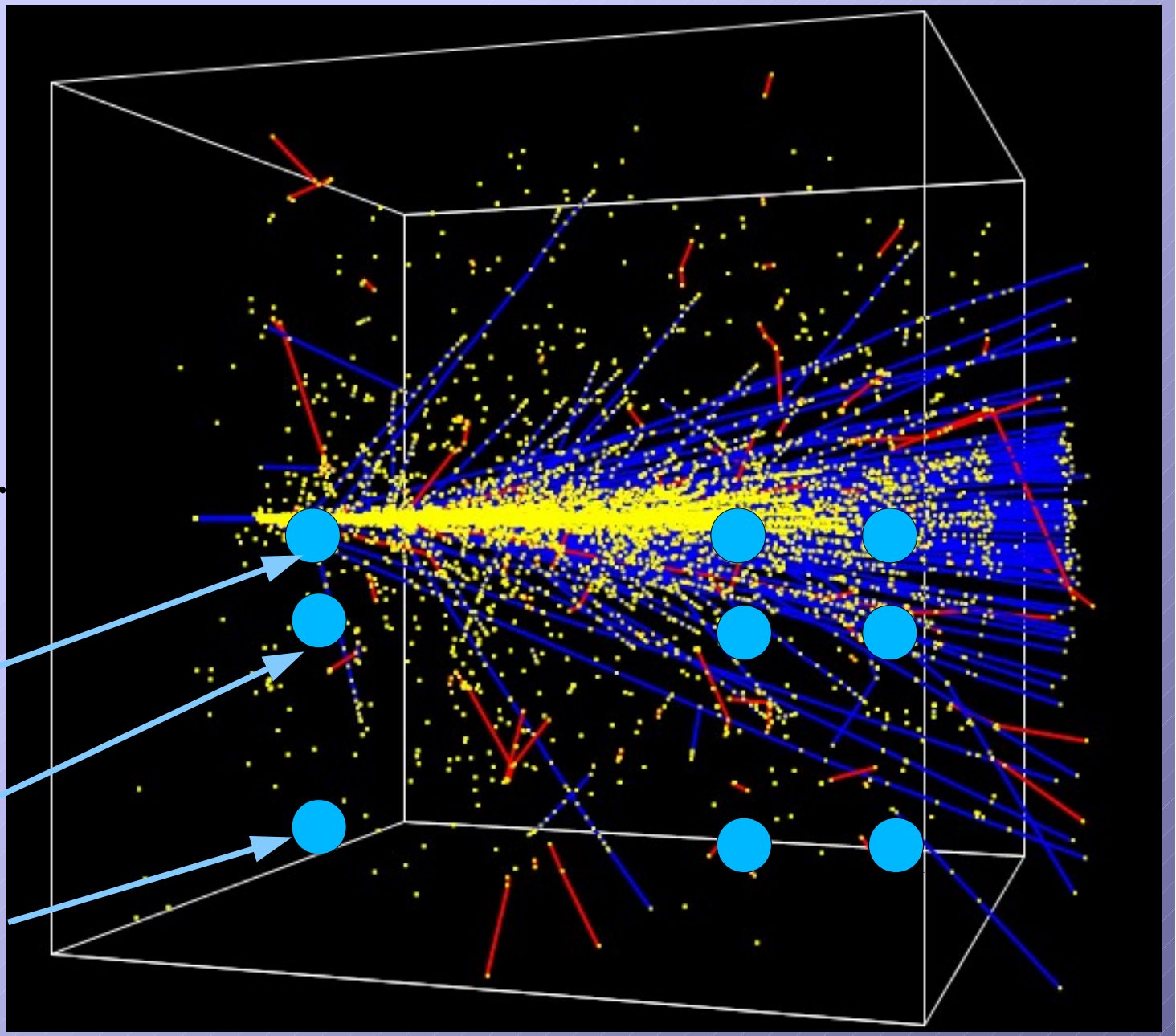
The saturation parameter: $y_0 = 150\ \mathrm{keV}/\mu\mathrm{m}$ (Kase *et al.* 2006)

4. Simulation of microdosimetric spectra

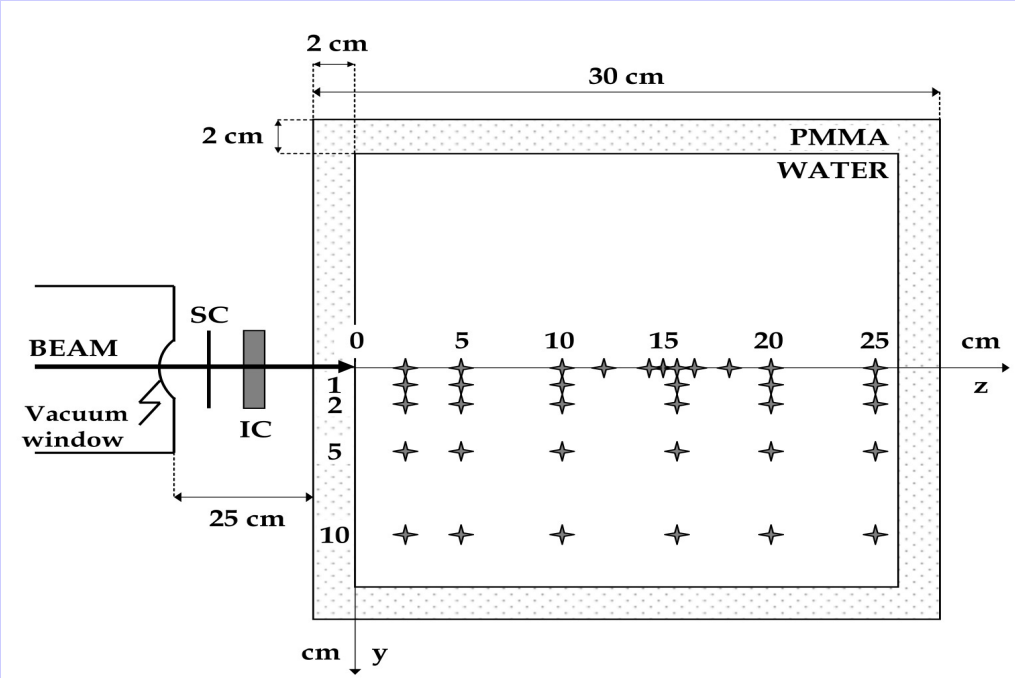
MCHIT simulations: TEPC in water

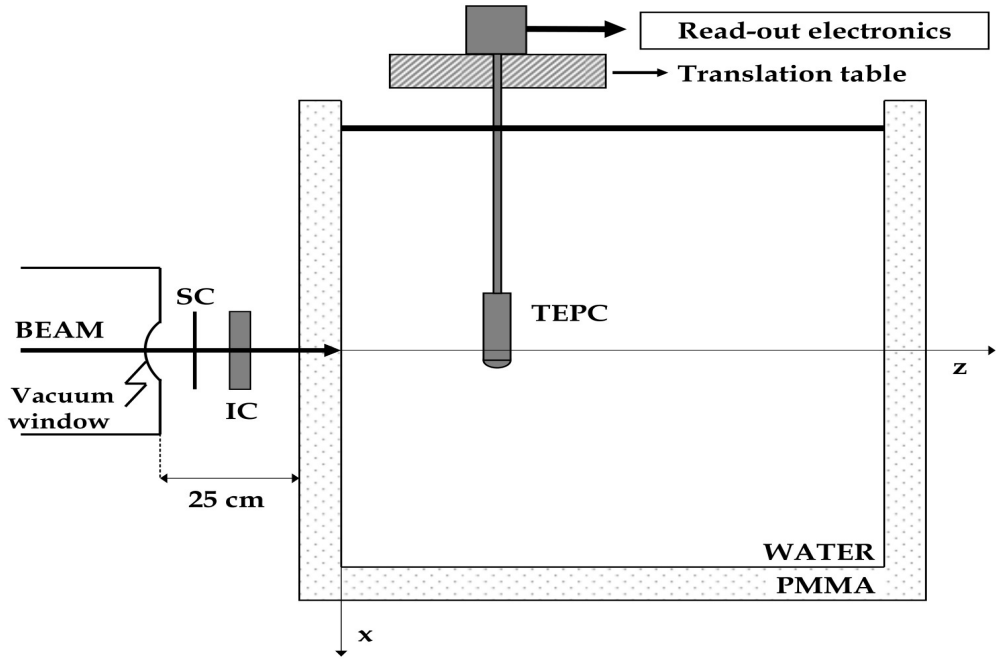
The detectors are placed at different positions relative to the beam.

The number of tracks in the TEPC per beam particle changes from ~1 at beam axis to $3*10^{-5}$ far from the beam axis.



Production of fragments in a water phantom



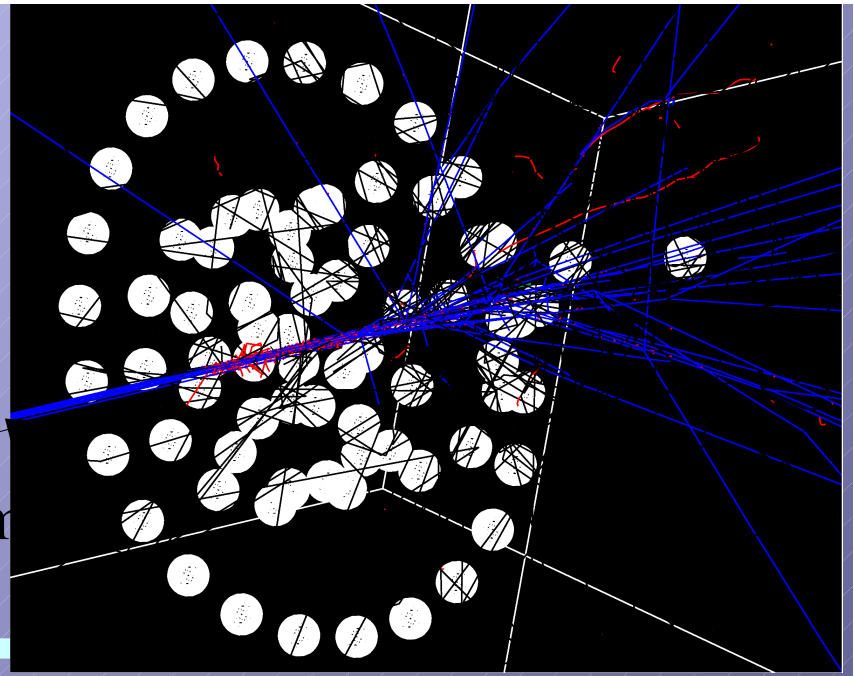


Experiment: 300A MeV ^{12}C beam in water, TEPC counter placed at various positions

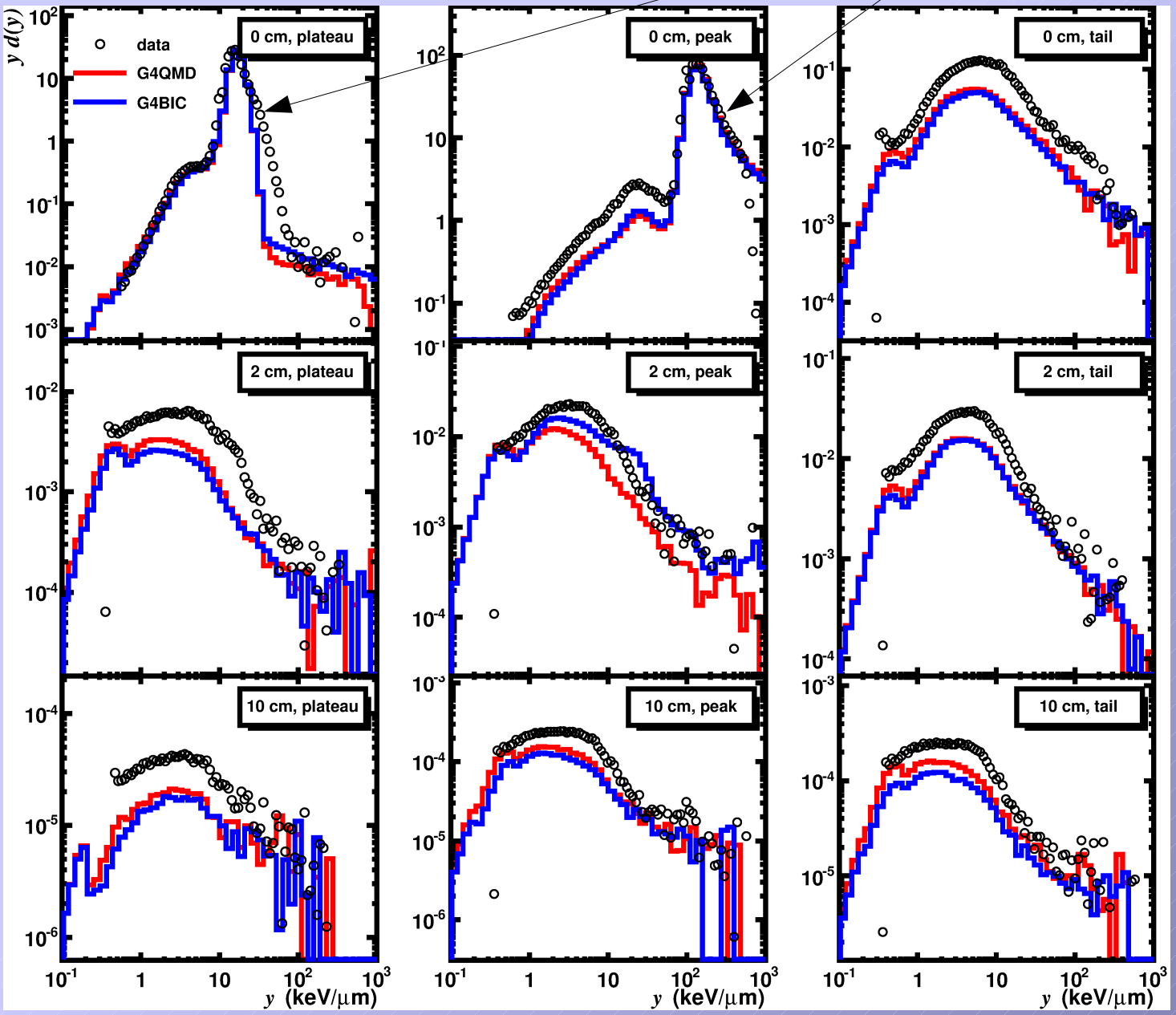
G. Martino, M. Durante, D. Schardt

PMB 55 (2010) 3441

In our simulations each TEPC counter is replaced by a ring to reduce the number of Monte Carlo histories.Than the result is accordingly rescaled.



Lineal energy spectra inside the phantom (in- and out-of-field)



Presented **per beam particle,** not per TEPC event.

Underestimation of event rates far from the beam: G4QMD and G4BIC fragmentation models have to be improved.

The shapes of the spectra are described well.

Simulation of microdosimetry spectra: ^{4}He, ^{7}Li and ^{12}C beams in water

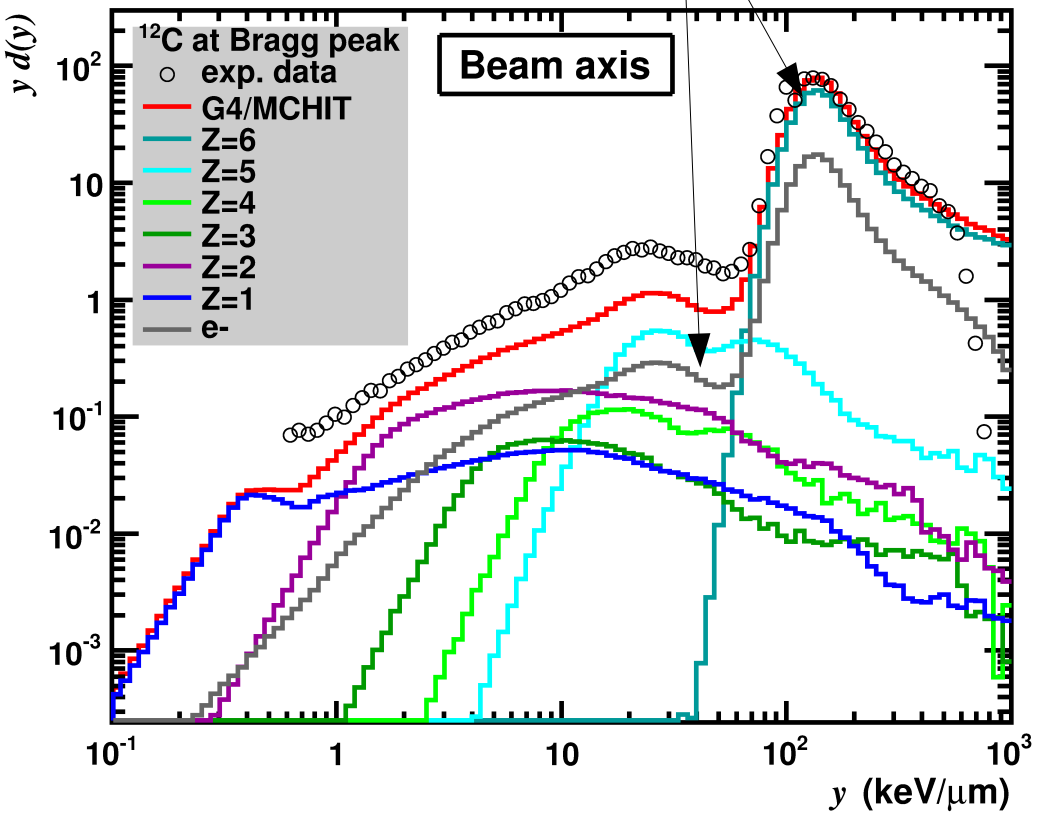
Lucas Burigo

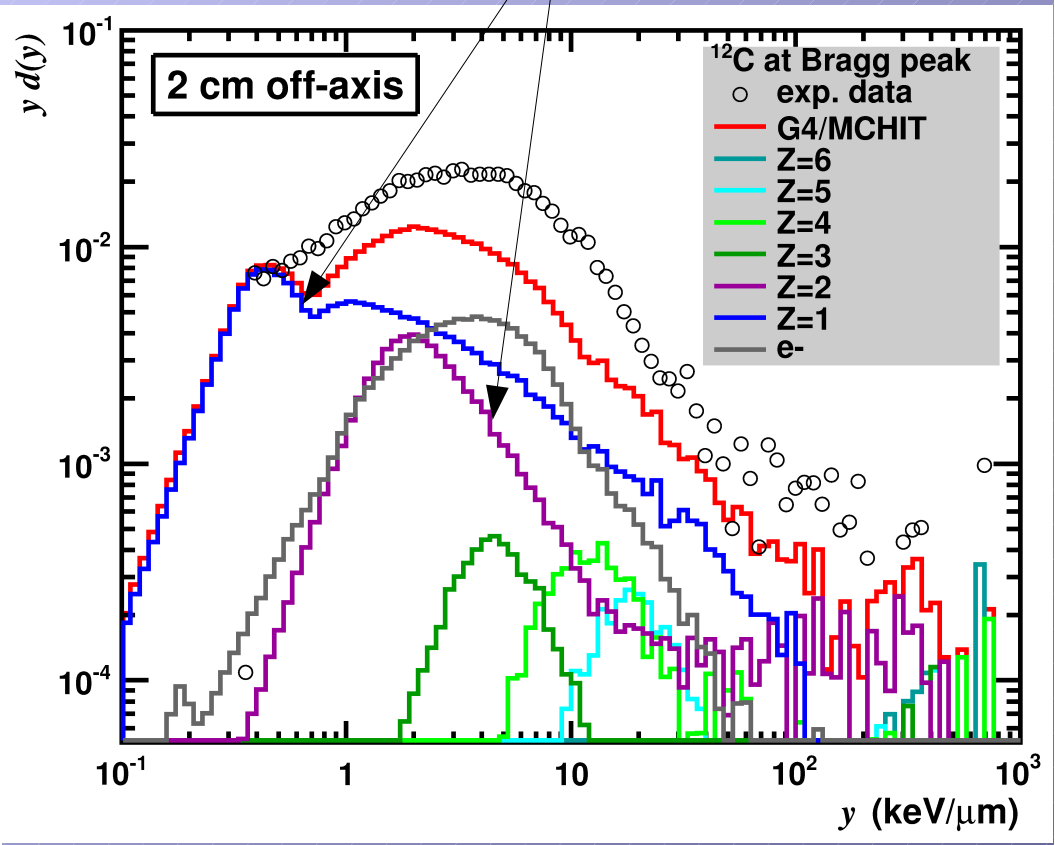
Contributions of specific fragments are identified in the calculated spectra: **very complicated mixture!**

*L. Burigo et al., NIMB **320** (2014) 89–99.*

Carbon, boron at the Bragg peak on the beam axis

Protons and helium nuclei off-axis





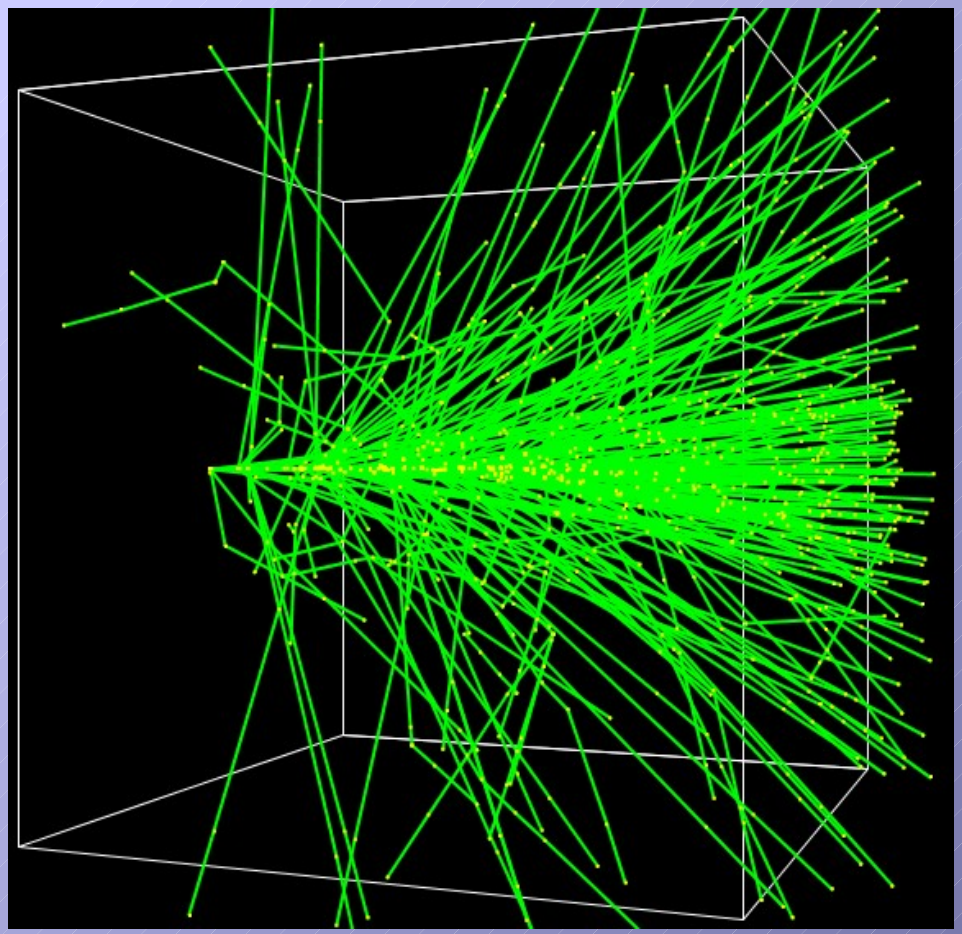
Conclusions on fragmentation

- **The calculations of microdosimetry spectra in the mixed fields is a certain challenge to theory, but the MCHIT model describes well the general shapes of microdosimetry distributions in- and out of the therapeutic ^{12}C beam.**

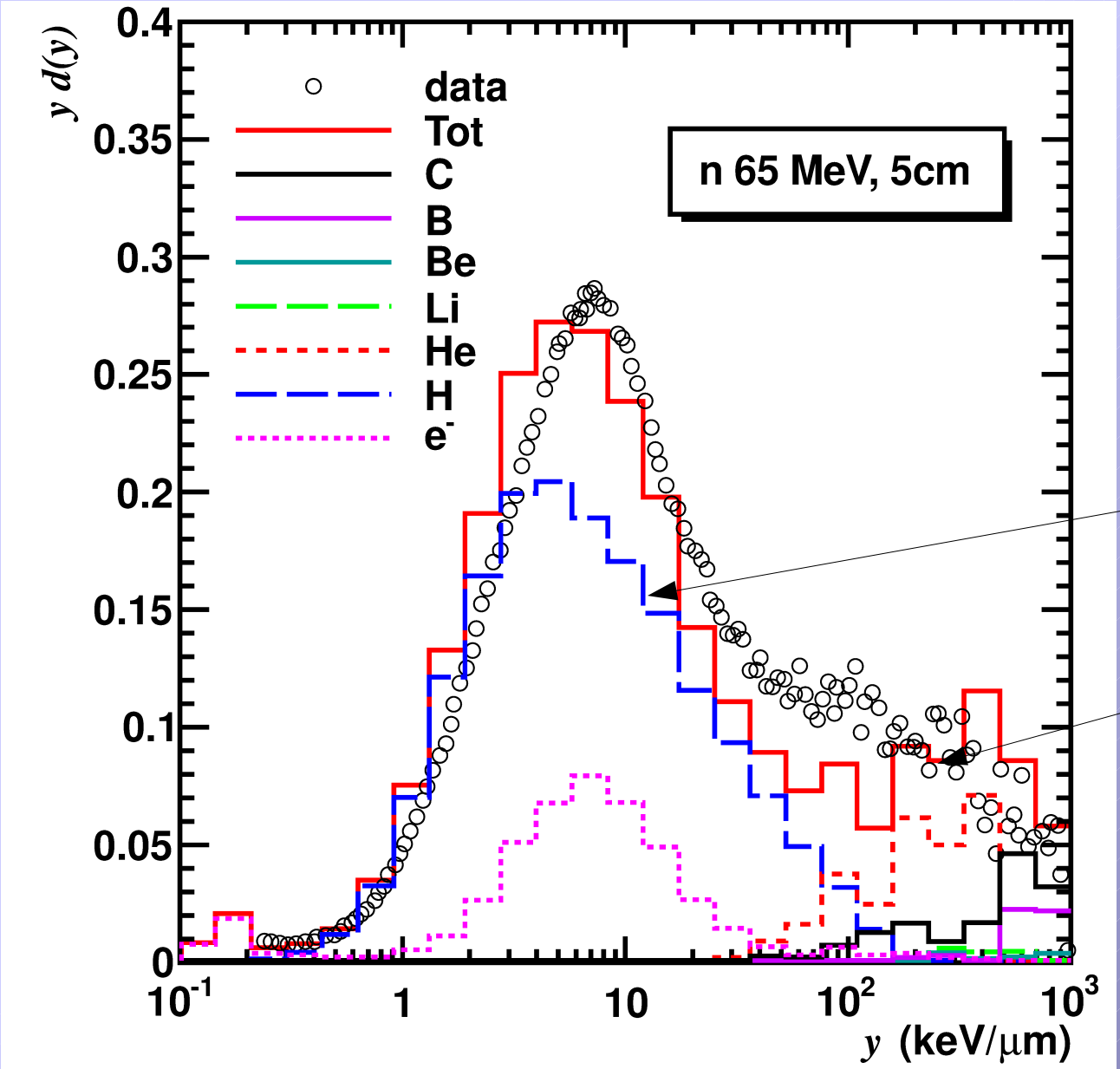
- **Improvements in Geant4 fragmentation models with respect to the production of protons, neutrons and alpha particles are necessary. This will help to describe the spectra far from the beam, e.g. at 10 cm radii.**

- **The doses at the radii of ~10 cm are calculated as 10^{-4} -10^{-5} of the therapeutic dose, and the contribution of high-LET neutrons reaches ~44%. This provides information for estimations of biological effects of secondary particles far from the therapeutic beam.**

Secondary neutrons



MCHIT validation: microdosimetry spectra from quasimonoenergetic neutrons



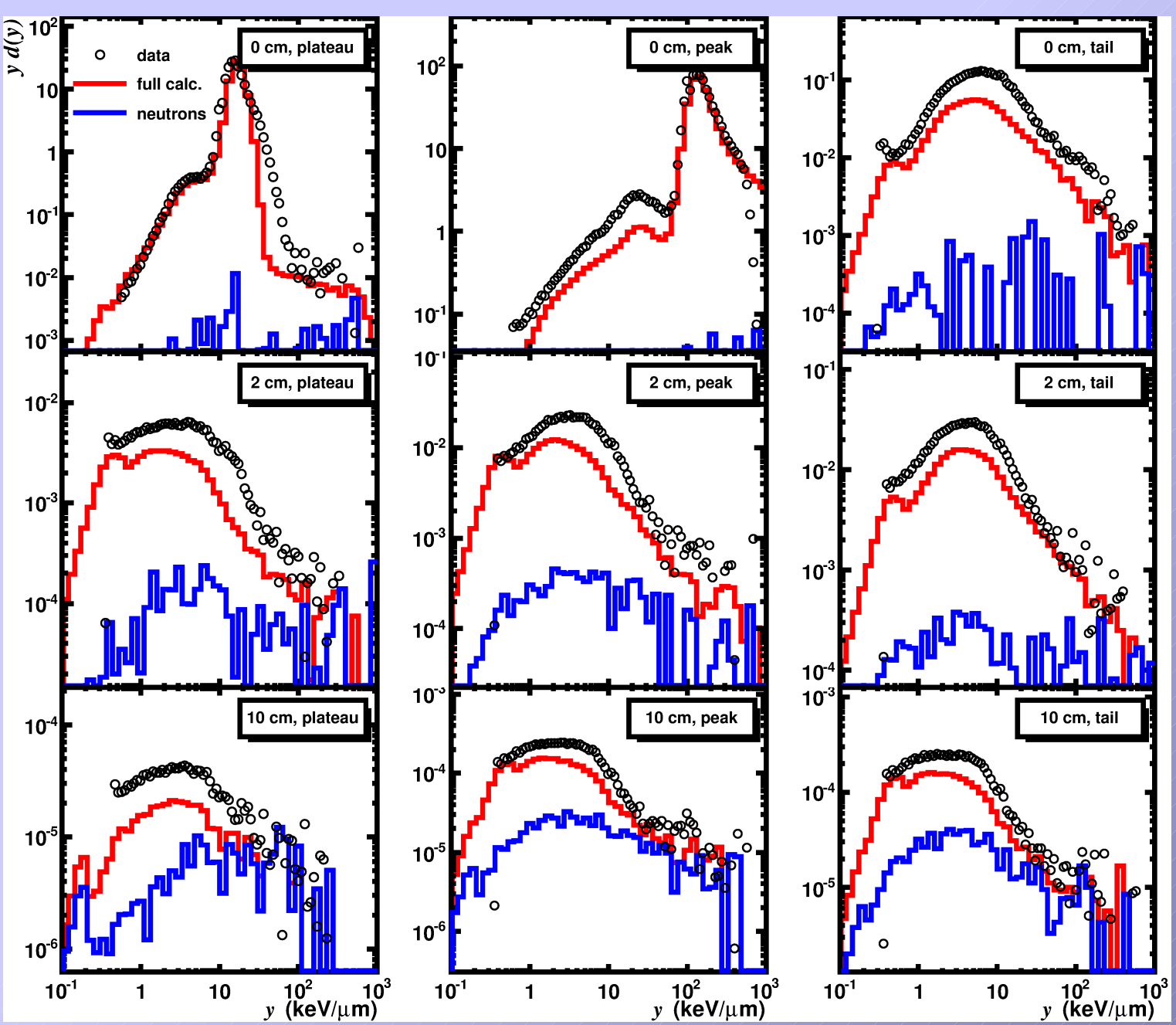
Quasimonoenergetic 65 MeV neutron beam in PMMA phantom, TEPC at 5 cm depth

Data: Y.Nakane, Y.Sakamoto, NIM A 459(2001)552

As expected, the largest contribution is due to protons, but helium and carbon nuclei build the tail at large *y*.

This good agreement gives confidence in estimating the response to secondary neutrons also in carbon therapy.

Calculated neutron contribution from ^{12}C beam



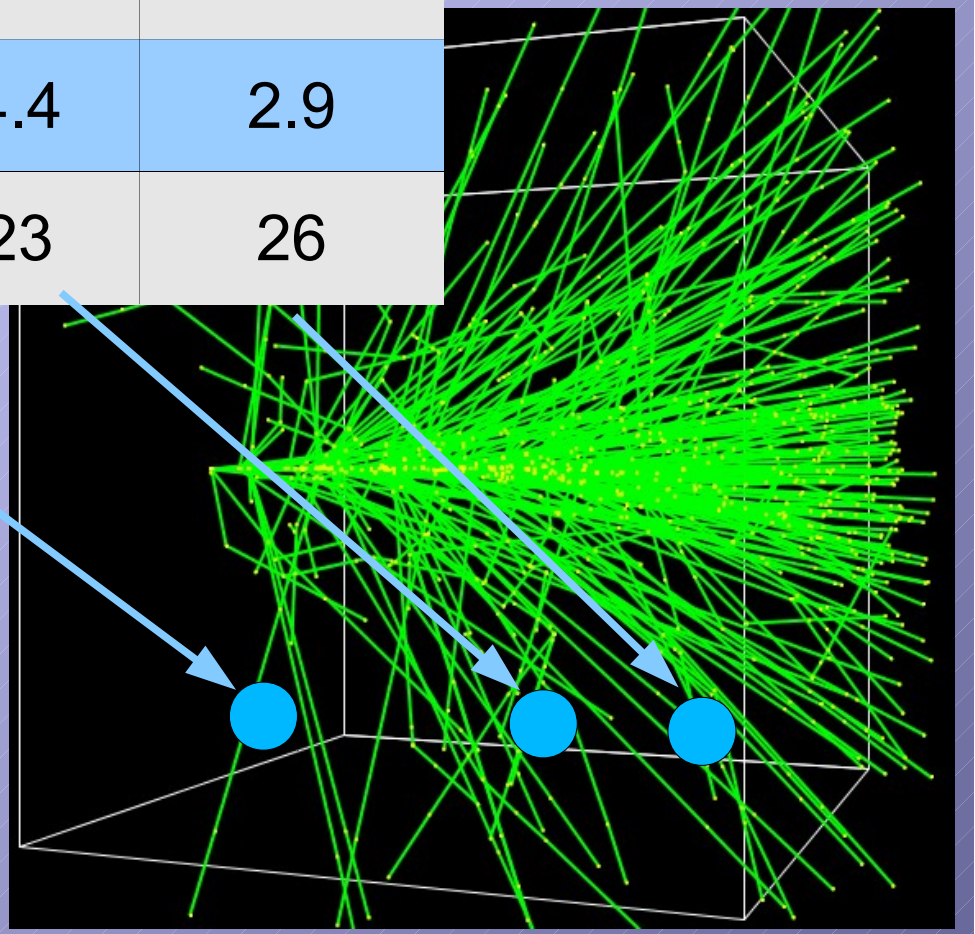
300A MeV ^{12}C beam in water

Obtained as a difference between two runs: with and without neutron interactions.

Burigo et al. 2012

Calculated neutron contribution to the total dose at several positions

in %		depth		
		plateau	peak	tail
radius	0 cm	<0.03	<0.06	0.6
	2 cm	5.5	4.4	2.9
	10 cm	44	23	26



Note the large values far from the beam where heavy nuclear fragments and partially protons are already stopped.

Remarks on secondary neutrons

- **The total dose from neutrons in the whole phantom was estimated with MCHIT (*Pshenichnov et al., PMB 50 (2005) 5493*) as ~1% of the ^{12}C treatment dose. This is similar to the dose from secondary neutrons in proton therapy.**

- **The number of neutrons produced by a single ^{12}C nucleus is larger than by a beam proton, but the therapeutic dose per beam particle is accordingly larger for ^{12}C. Therefore the neutron contribution to therapeutic dose remains comparable in both cases.**

- **This estimation agrees well with GSI data collected few years later, see *K. Gunzert-Marx et. al, New J. of Phys. 10 (2008) 075003***

- **Due to a potentially high RBE for neutrons (see e.g. *W.Newhauser, M.Durante, Nature Rev. Cancer 11(2011)438*) the distribution of neutron dose has to be thoroughly characterized. This can be done, in particular, by microdosimetric measurements and simulations.**

Conclusions on microdosimetry

- **"Experiments and calculations of microdosimetric spectra play complementary roles. The degree of agreement between experiment and theory serves as a test of the validity of both." (ICRU-36 Report)**

- **Traditional TEPCs, known already for 50 years, were now simulated with modern Geant4/MCHIT code. Some deficiencies of existing models have been localied.**

- **Despite of the simplicity of the TEPC, it provides valuable information on the composition of a complex radiation field when the data are combined with MC simulations.**

5. Spread Out Bragg Peak (SOBP)

Profiles of energy deposition and y*

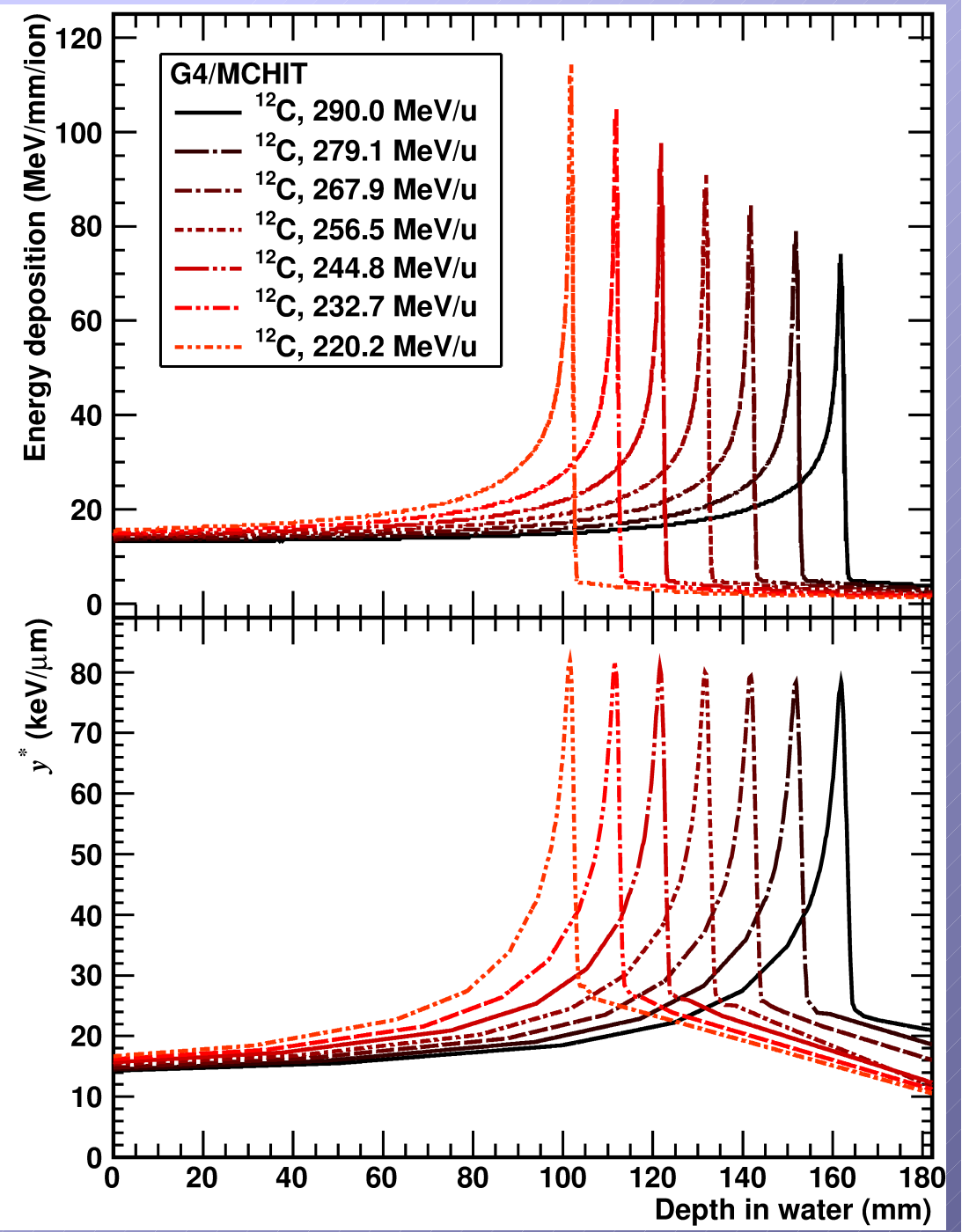
For a set of beams of different energy the resulting dose is obtained as a sum of individual contributios

$$D_{total} = \sum w_i D_i ,$$

where D_i is the dose provided by an individual beam and w_i is its weght.

MCHIT provides a library of dose profiles together with corresponding y^* tables for specific beam energies and ions.

Then RBE is calculated using the MKM model.



Survival fractions for mixed beams

According to the theory of dual radiation action (*Zaider and Rossi 1980*) the cell survival after the application of the total physical dose *D* of a *mixed* field can be calculated as:

$$S_{mix}(D) = \exp\left(-\alpha_{mix} D - \beta_{mix} D^2\right)$$

$$\alpha_{mix} = \sum_i f_i \alpha_i$$

$$\sqrt{\beta_{mix}} = \sum_i f_i \sqrt{\beta_i}$$

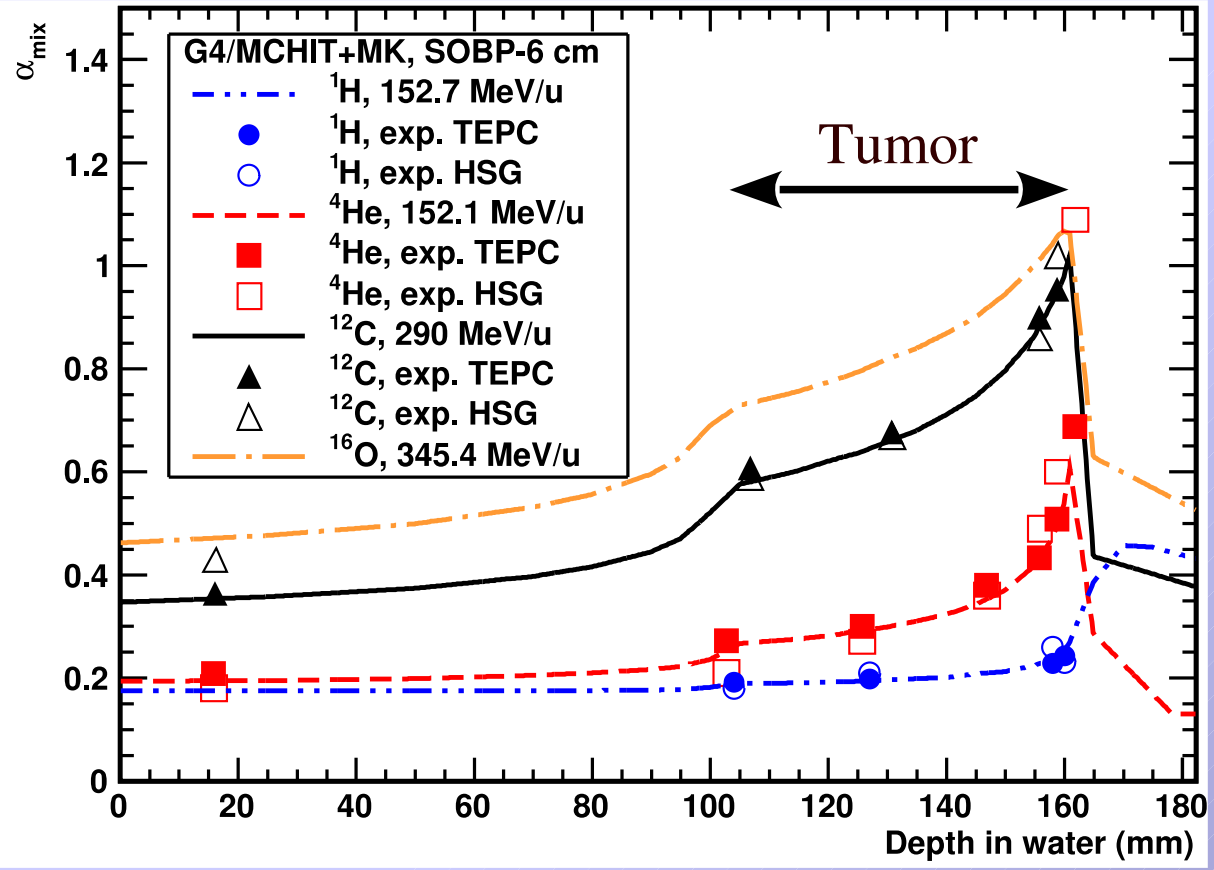
Here f_i is the weight coefficient (fraction) of the local physical dose of the *i*-th monoenergetic beam, while α_i and β_i are the parameters of the LQ model specific to the *i*-th beam.

Resulting RBE_{mix} for the mixed radiation is calculated for the survival fraction of cells $S_{mix}(D)$ and it also depends on the depth. Finally, the biological (RBE-weighted) dose D_{bio} is calculated from RBE_{mix} and physical dose:

$$D_{bio} = RBE_{mix}\, D.$$

We developed an efficient algorithm to obtain f_i for a given SOBP with a flat biological dose in the tumor.

Calculated and measured α_{mix} profiles



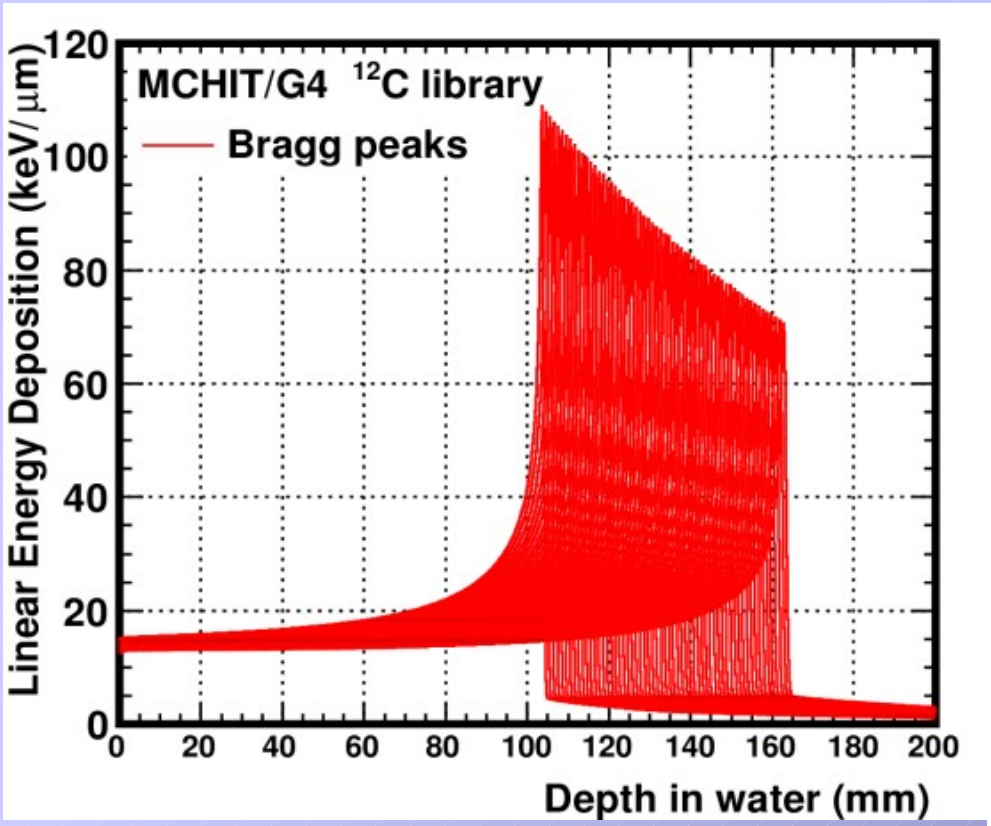
Burigo, Pshenichnov, Mishustin, Bleicher,
Phys. Med. Biol. ***60*** *(2015) 3313*

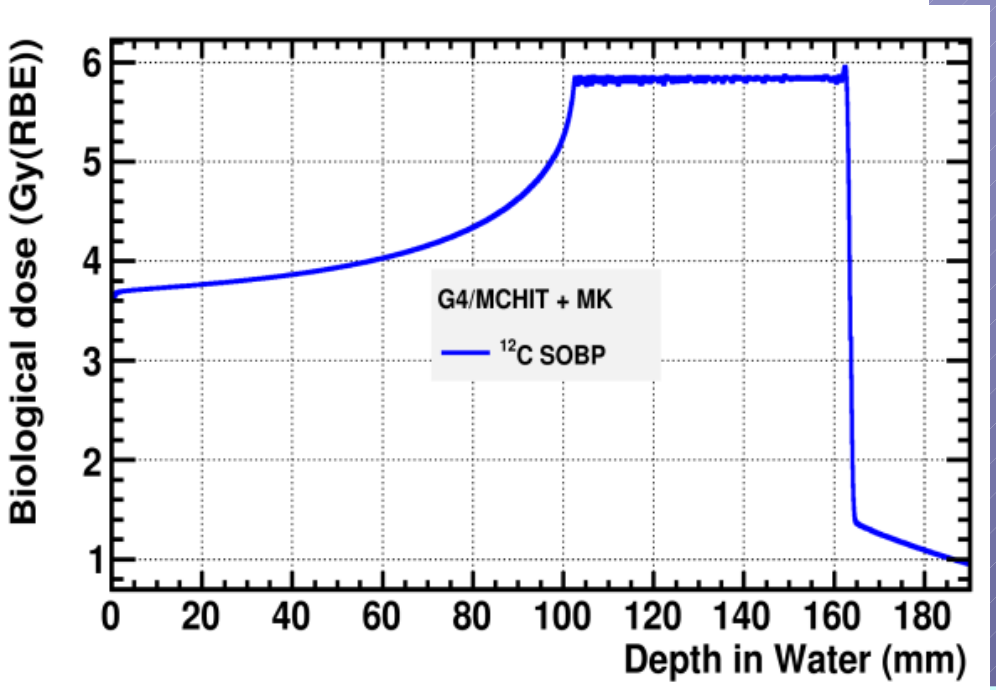
Calculated depth profiles of α_{mix} for ^{1}H, ^{4}He and ^{12}C agree well with the data collected at HIMAC, Japan for survival of Human Salivary Gland (HSG) cells and also with α_{mix} extracted from measured *y.**

Therefore, we are confident in calculating cell survival profiles for ^{1}H, ^{4}He and ^{12}C and can also extrapolate to ^{16}O.

Irradiation of an extended tumor

- A set of beam energies is needed to cover the volume of the tumor uniformly, i. e. Spread-out Bragg Peak (SOBP)
- Aim of the study is to calculate an optimum superposition of Bragg peaks for a homogeneous survival fraction over a given volume of tumour tissue and to analyse the depth and radial dose profiles of different ions

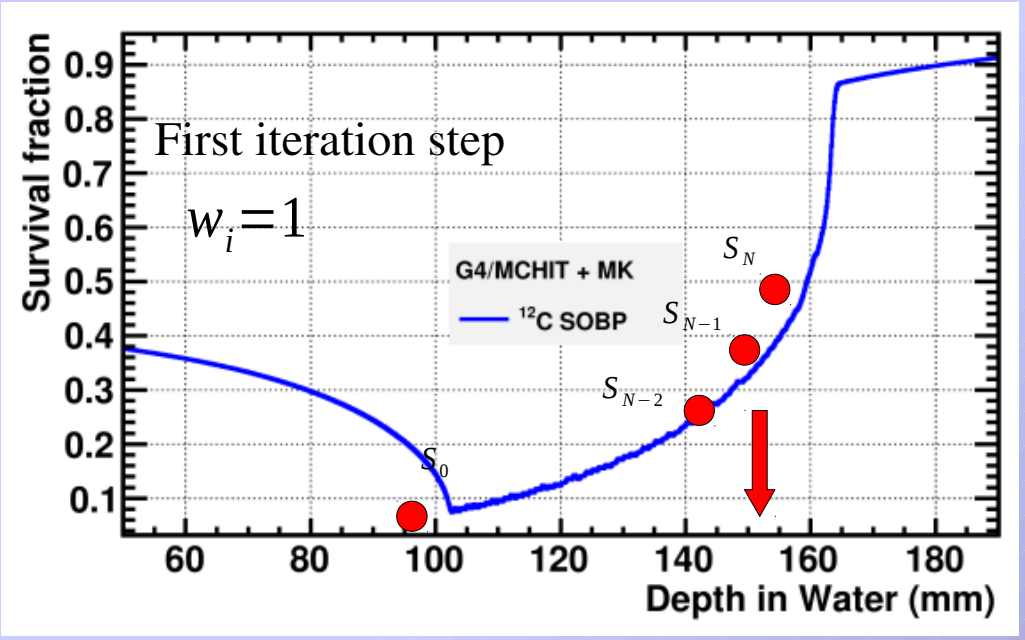


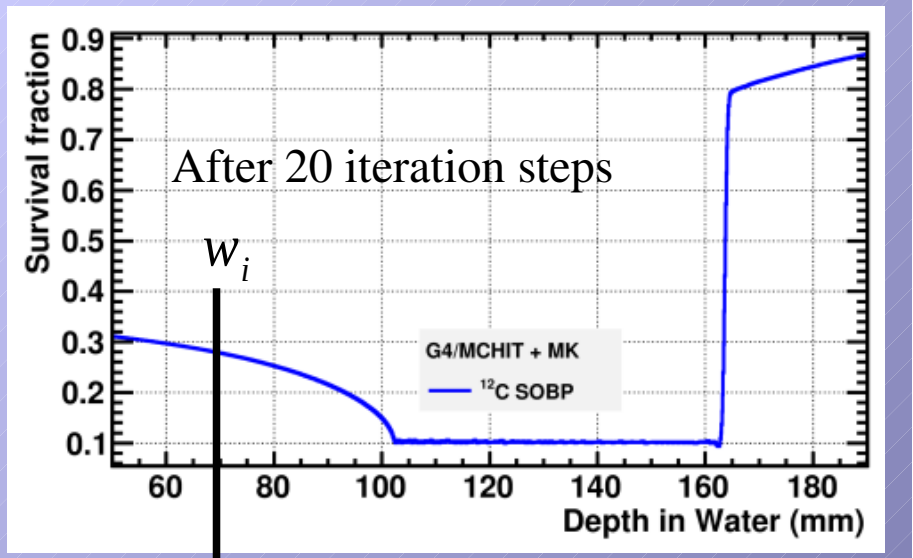


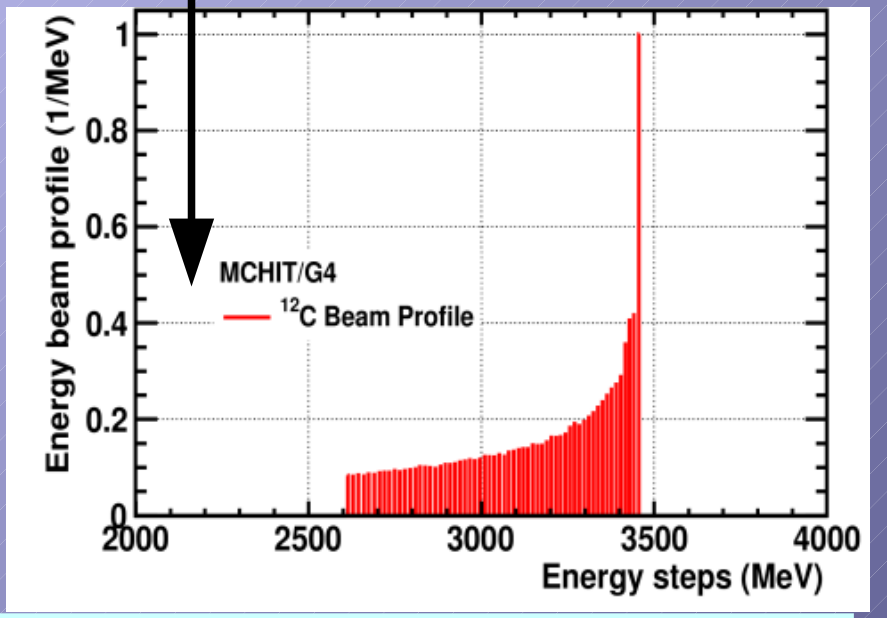
$$Biological\ dose = RBE \cdot D_I$$

SOBP optimization

- **Optimization problem is solved by calculating $\{w_i\}$, which produce a flat**
- **survival fraction**







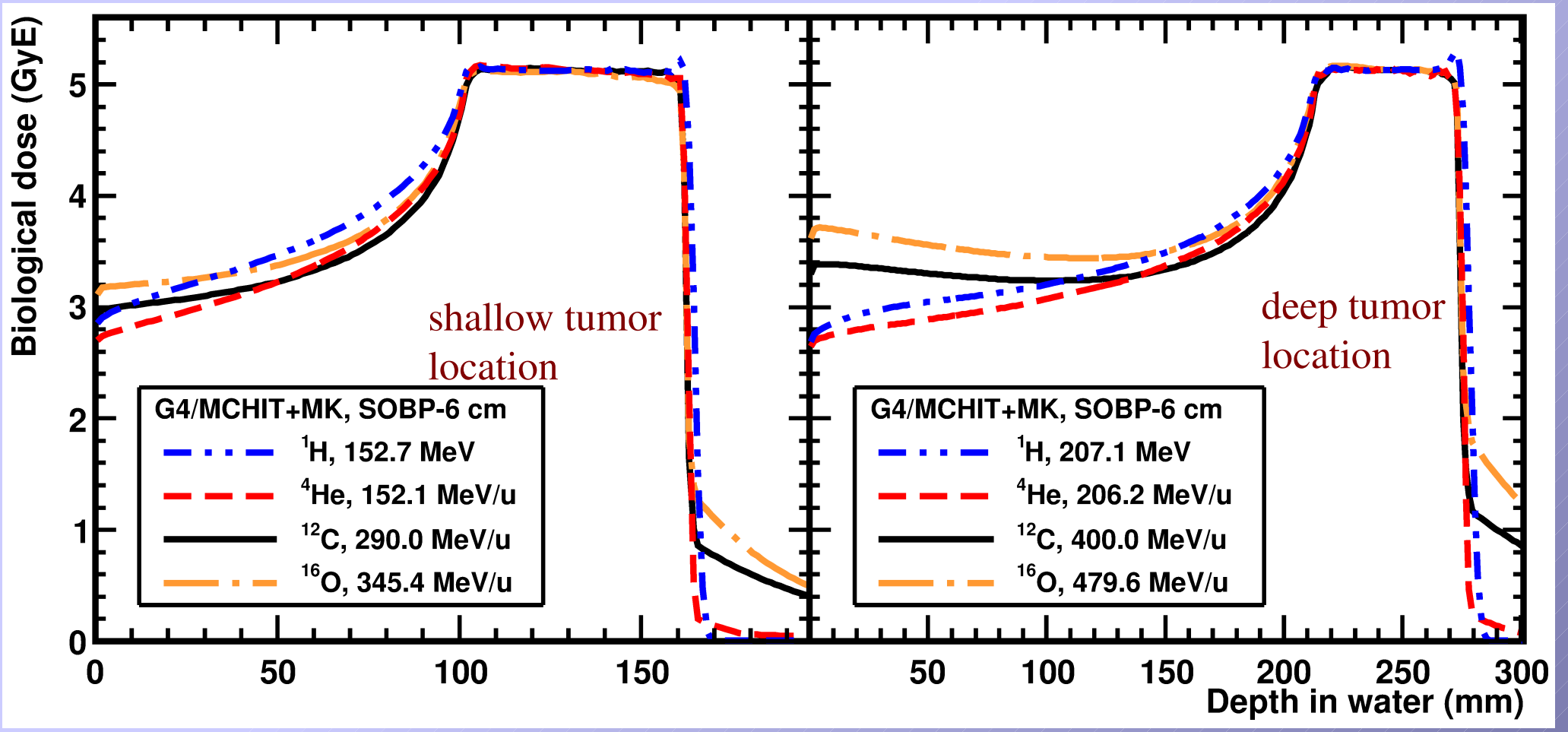
1) Total physical dose: $D_{total} = \sum_{i=1}^{N} w_i \cdot D_i$

2) Survival fraction: $S = \exp\left(-\alpha_{mix} D_{total} - \beta D_{total}^2\right)$

3) Ratio of survival values: $s_i = S_i / S_0$

4) Weighting factor for physical dose: $w_i = w_i \cdot s_i$

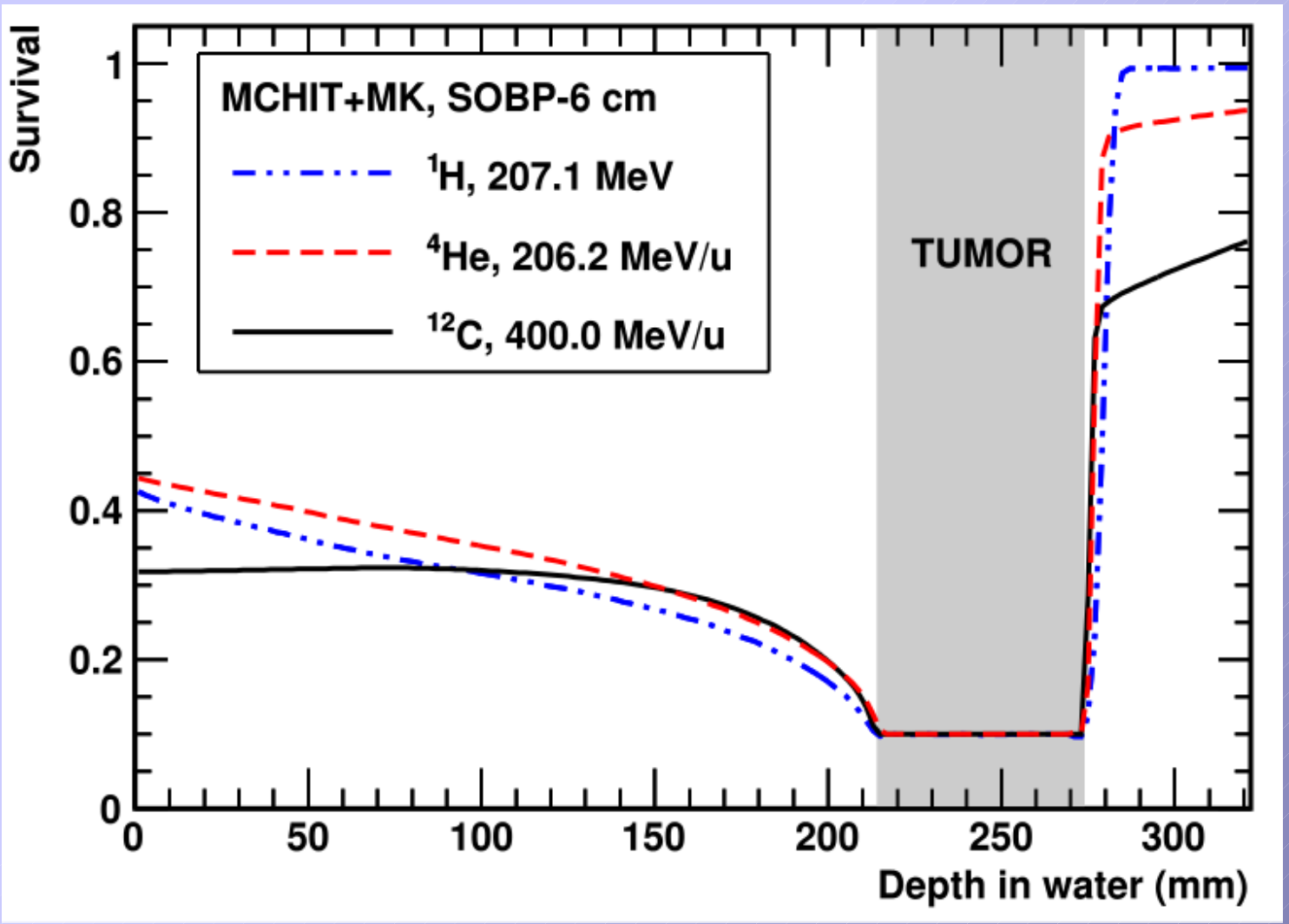
Biological (RBE-weighted) dose



- **Despite of the difference in RBE between different ions, their SOBP distributions can be tuned to provide the same biological dose in the tumor volume.**
- **Some advantages of ^{4}He can be seen: higher survival of healthy tissues than in ^{1}H, but smaller fragmentation tail than in ^{12}C (10% effect!).**

Burigo, Pshenichnov, Mishustin, Bleicher, Phys. Med. Biol. ***60*** *(2015) 3313*

Comparison of various ion beams



- ^{4}He beams can be considered as a promising ion-therapy option in addition to presently used ^{1}H and ^{12}C.
- Further studies are needed, e.g. with multiple fields.

Calculation of cell survival fractions for several combinations of healthy and tumor tissues

Sensitive:

$$(\alpha/\beta)_{\mathrm{X-rays}} = 10 \text{ Gy}$$

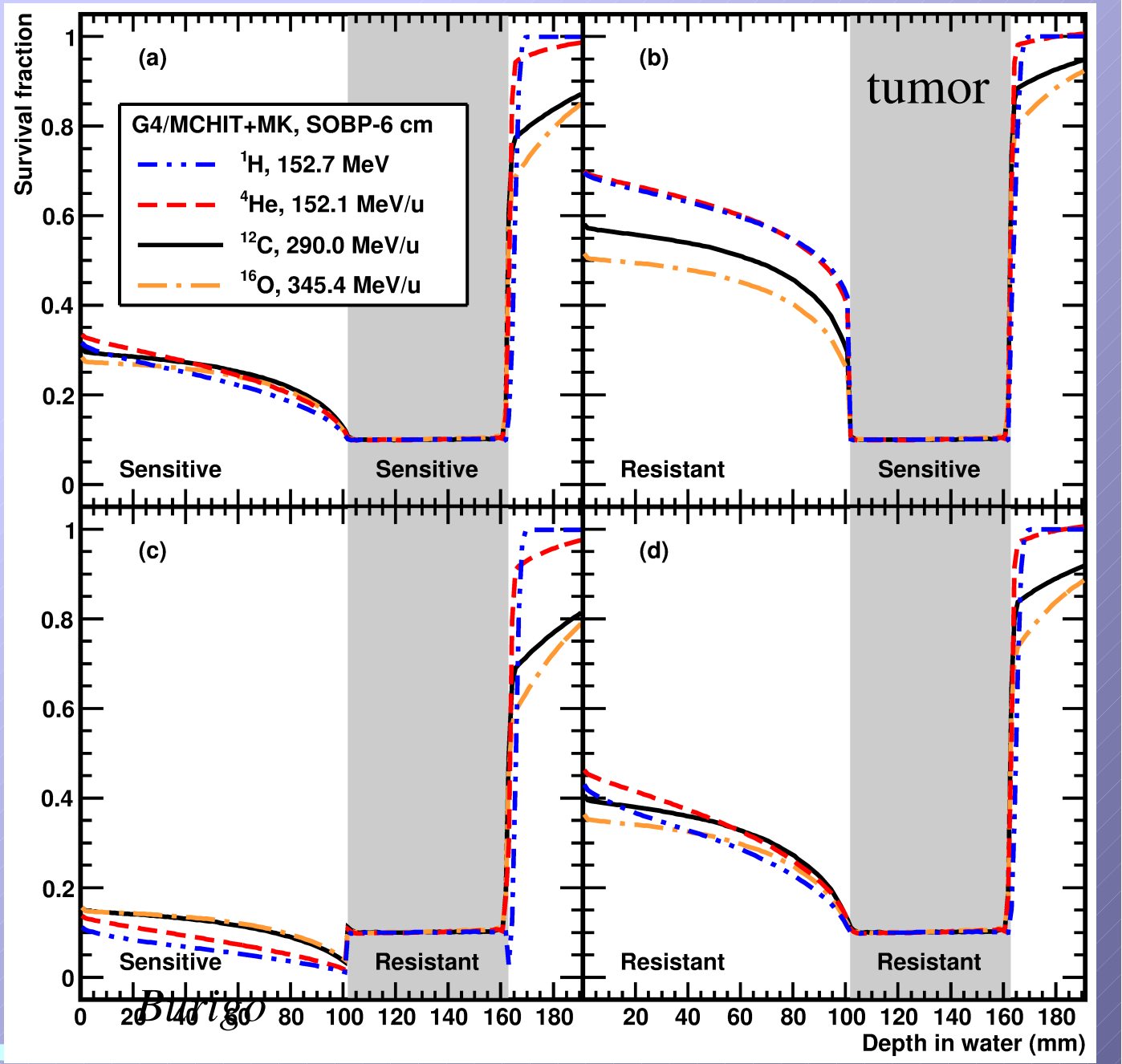
Normal (HSG):

$$(\alpha/\beta)_{\mathrm{X-rays}} = 3.8 \text{ Gy}$$

Resistant:

$$(\alpha/\beta)_{\mathrm{X-rays}} = 2 \text{ Gy}$$

*Burigo, Pshenichnov, Mishustin, Bleicher, PMB. **60** (2015) 3313*

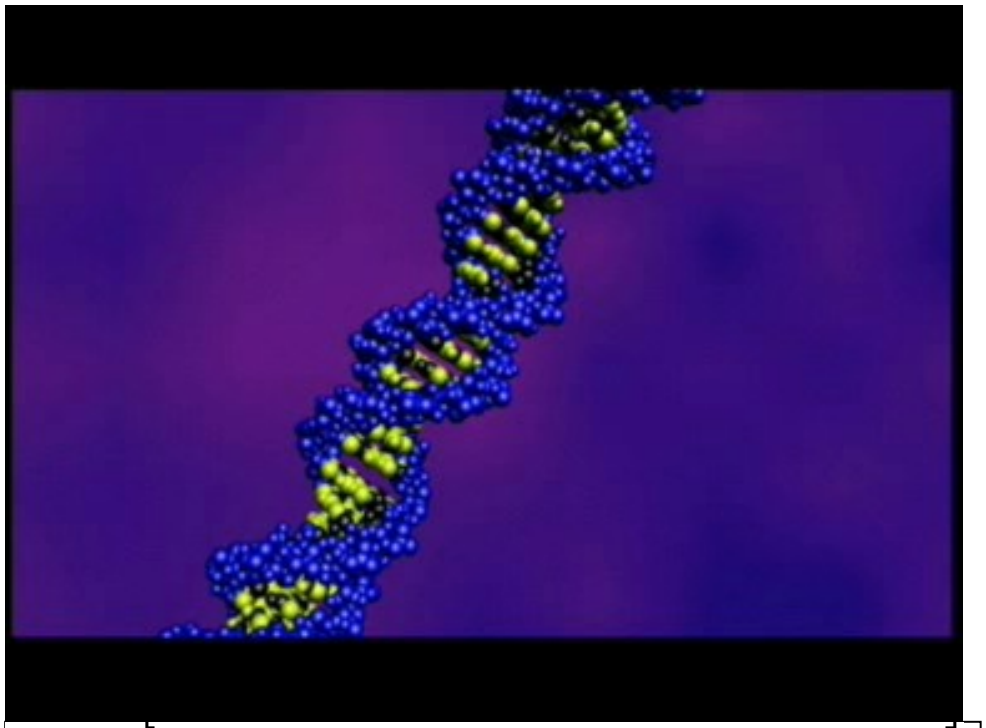


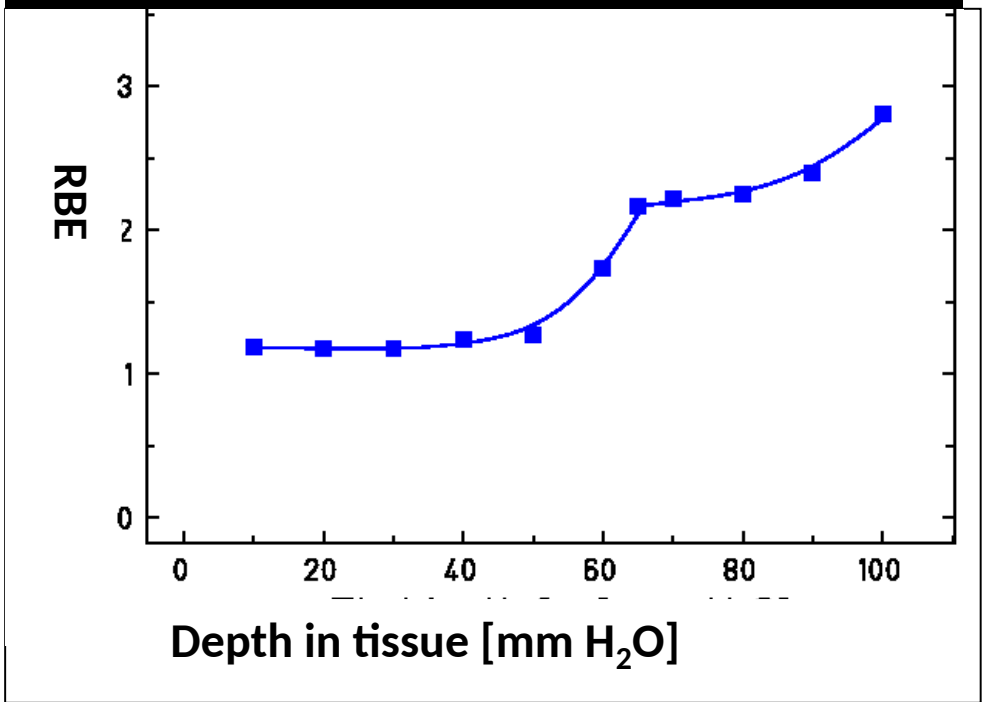
Conclusions on beam choice

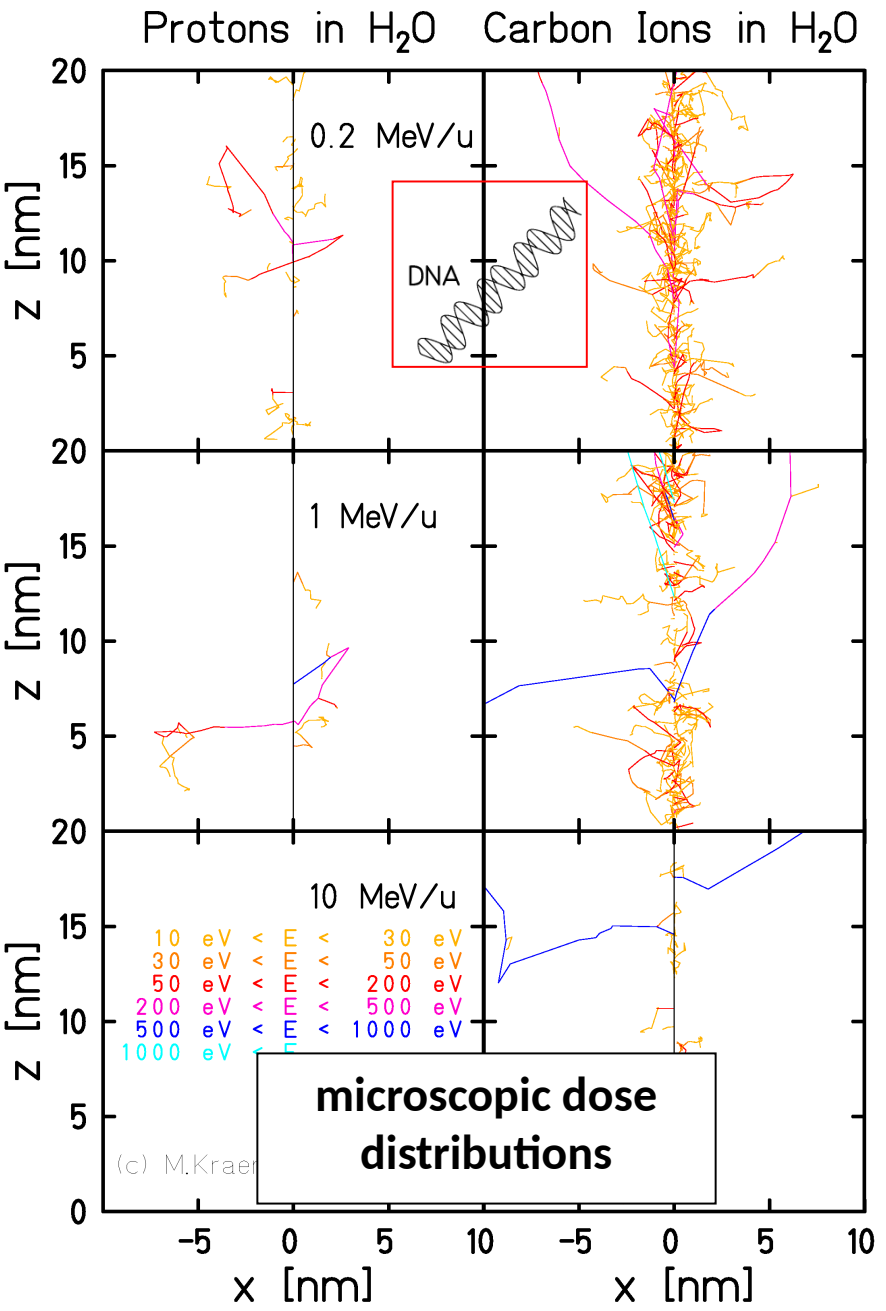
- **Theoretical modelling is needed to find the optimum ion beam for specific treatment**
- **Selection of ions depends on the position of the tumor and organs at risk**
- **Protons better spare tissues behind the tumour**
- **Heavier ions better spare tissues alongside the tumour**
- **Helium ions might provide the best compromise**

6. Track structure and nanodosimetry

Radiation effects on bio-molelcular level







Monte-Carlo track structure codes

Monte-Carlo track structure codes use the detailed history Monte Carlo approach to simulate the trajectory of ionizing particles through matter and the transport of all secondary electrons produced in the ionization events. Examples: PITS (*Wilson and Nikjoo, 1999*) and PARTRAC (*Friedland et al., 2003*)

In addition to simulations of the physical processes, some track structure codes also simulate the chemical processes of water radiolysis.

In our calculations we use Geant4-DNA packadge (*Incerti al., 2010*), which extends the Geant4 toolkit for track structure simulations. It accounts for the following interactions:

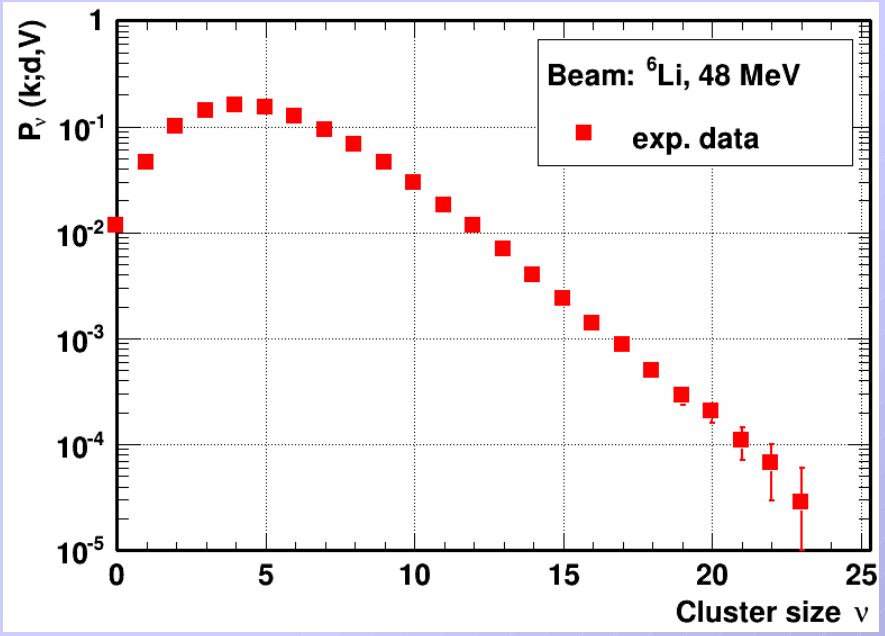
- for electrons
- **elastic scattering**
- **electronic excitation**
- **ionisation**
- **vibrational excitation**
- **attachment**

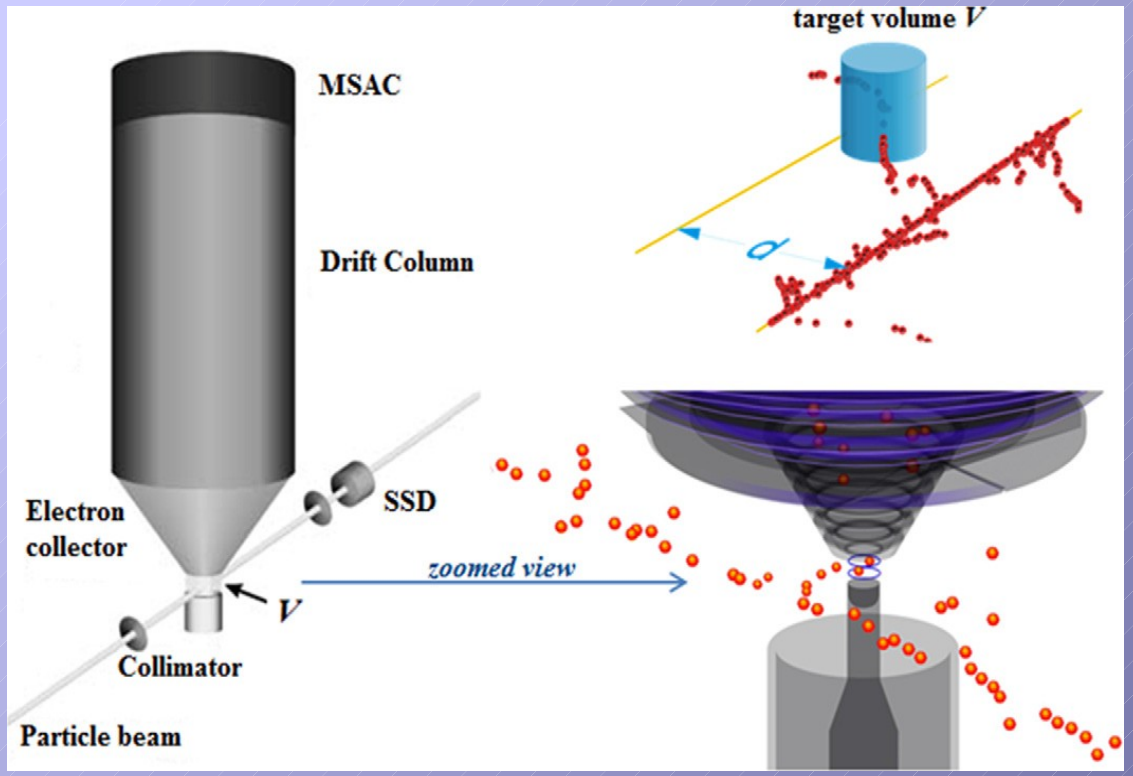
- for ions
- **electronic excitation**

ionisation
- **charge increase**
- **charge decrease**

Nanodosimetry technique

Nanodosimetry allows to measure the number of ionizations due to the passage of an ion through a nanometric target volume.





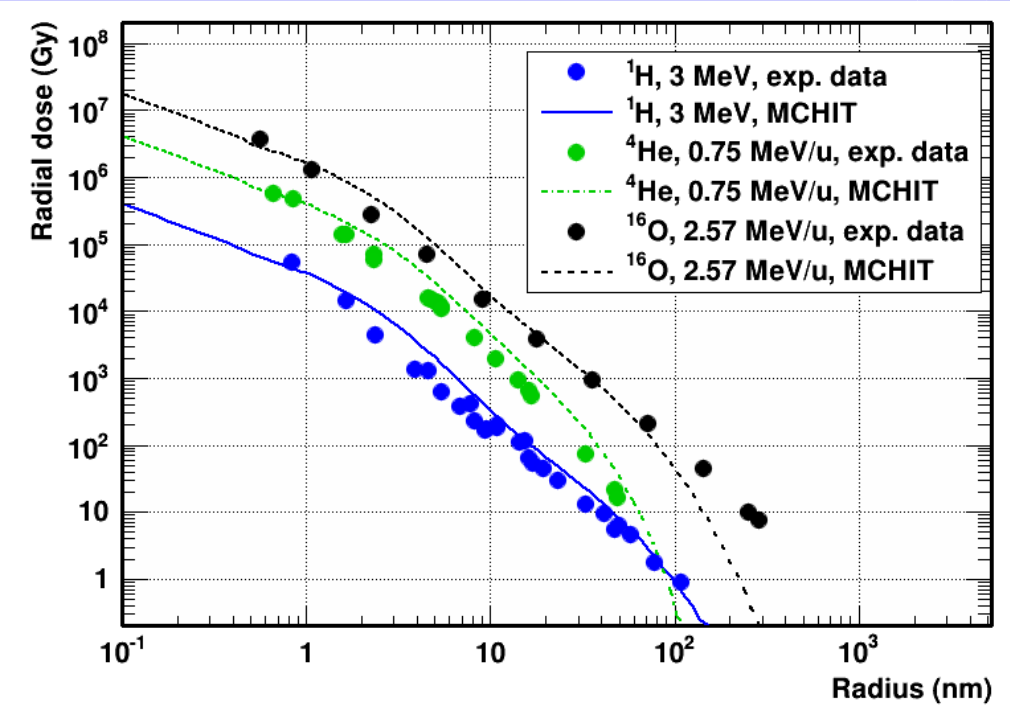
(Conte *et al.*, *New Journal of Physics* **14** 093010,2012)

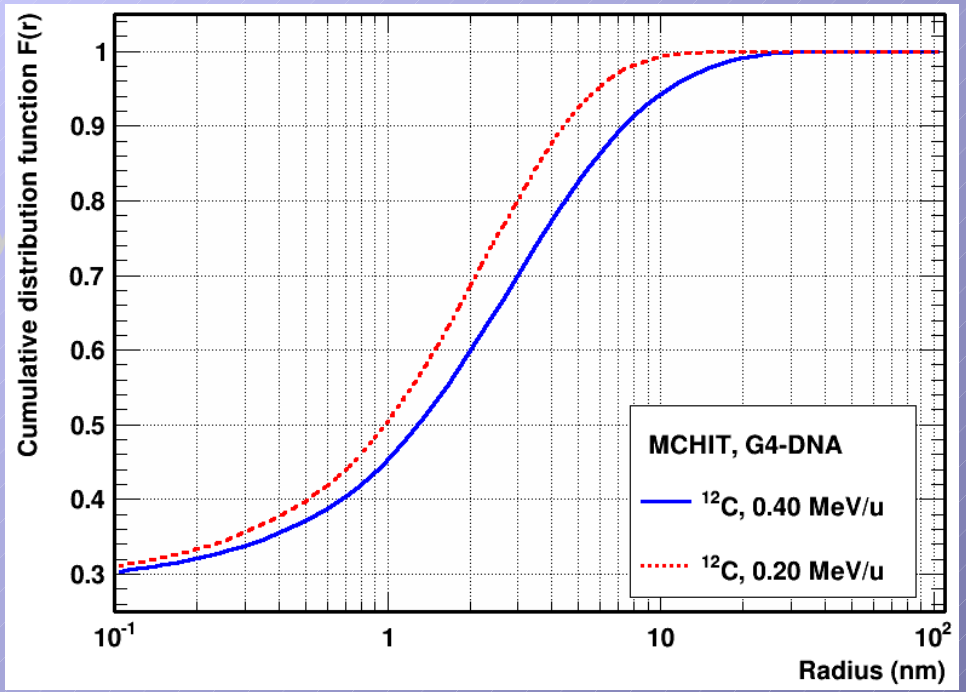
Experimental data from nanodosimetry can be applied to benchmark physical models used to investigate the clustering of DNA lesions.

Radial dose distributions around ion tracks

Recently MCHIT was extended to calculations of the ion energy deposition at the nanometer scale by using the Geant4-DNA package.

Now we are able to reproduce experimental data on radial dose profiles around an individual track in sub-cellular volumes traversed by ions.





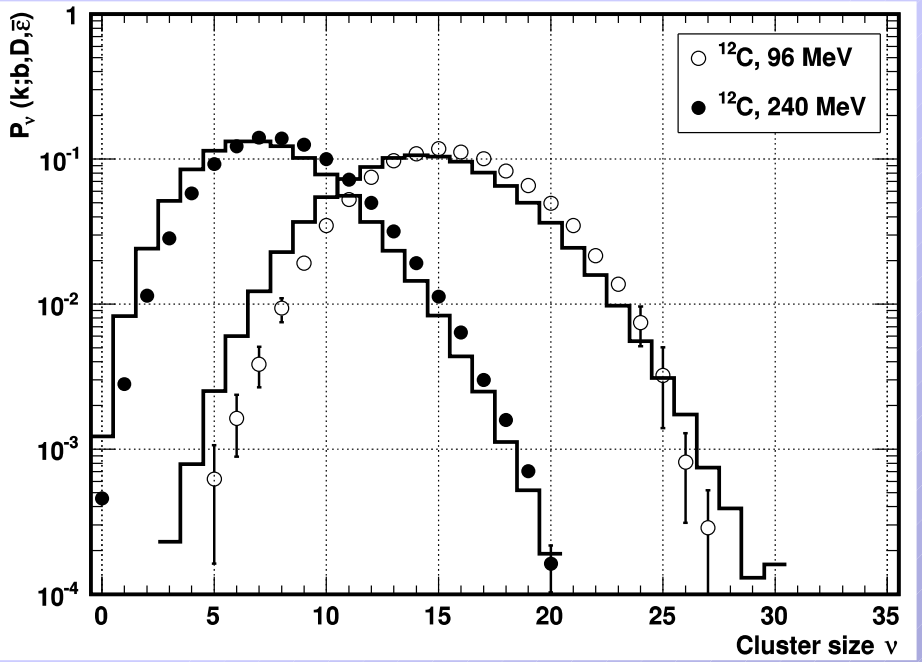
The cumulative distribution of energy deposition for slow carbon ions shows that about 30% of the energy deposition is delivered on the ion track, while the remaining 70% is distributed over more than 20 nm radius.

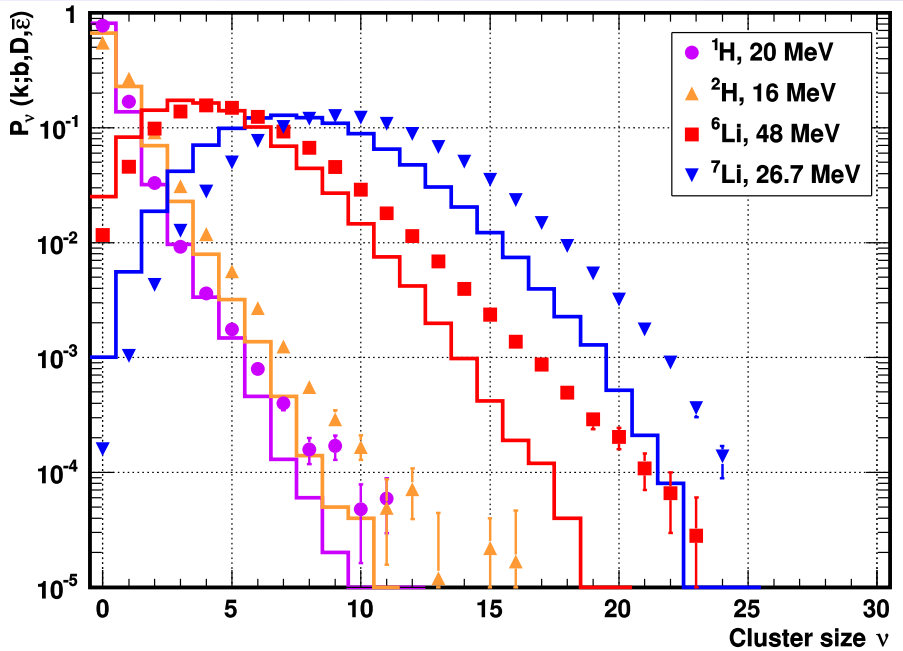
(Burigo, Pshenichnov, Mishustin, Hilgers, Bleicher, PMB 61 (2016) 3698, *featured PMB paper*)

Ionization cluster-size distributions

Measurements were done for ^{1}H, ^{2}H, ^{6}Li and ^{7}Li ions crossing a sensitive volume with the diameter of 20 nm at zero impact parameter.

MCHIT/Geant4-DNA results are shown by histograms, experimental data (Conte et al., 2012) are presented by various symbols.





Probability distributions of ionization cluster sizes induced by carbon ions are well reproduced. Distributions for lighter ions are also reproduced well, despite some underestimation of larger cluster sizes (contamination by slow ions).

Such nanodosimetry data can be used for modeling DNA damages.

Conclusions on nanodosimetry

- Careful characterization of ionization processes on nanometer scales is necessary to evaluate the radiation-induced DNA damage by therapeutic ion beams.
- Experimental nanodosimetry data for therapeutic ion beams are well reproduced by Monte Carlo simulations with MCHIT.
- Future work: couple MCHIT with radiobiological models to reproduce experimental yields of single and double strand breaks as well as to investigate the formation of more complex damages and the respective cell response.

Important general concusions

- **Each Treatment Planning System (TPS) requares inputs:**

  - physical models: physical dose distribution, especially in healthy tissues due to lateral beam spread and fragmentation tail;
  - radiobiological models: e.g. Local Effect Model (LEM) or MKM to calculate cell survival and RBE in mixed radiation fields;

- **"Unfortunately *ab initio* predictions of cell survival and the RBE values based on ion track physics are neither reliable, nor computationally feasible for years to come, due to lack of knowledge on the dominant biological processes associated with DNA damage and repair."**
  (Kraemer, Durante, Eur. Phys. J. D60 (2010) 195)

- **Further progress in the field of particle therapy is only possible via cooperation of physicists, biologists and medical doctors!**

Thank you for attention!