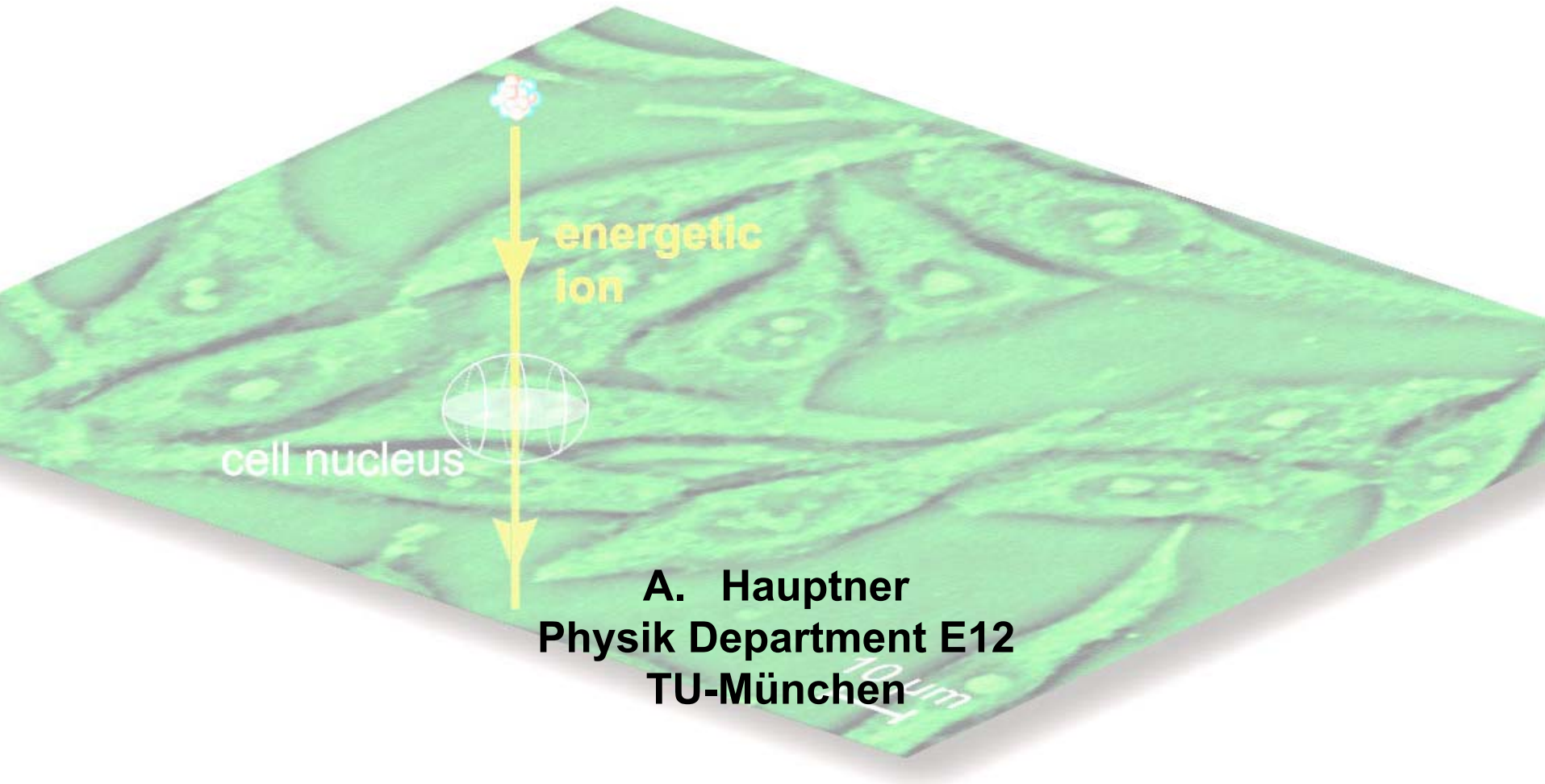
Damage structure along ion tracks in cell nuclei



A. Hauptner
Physik Department E12
TU-München

Motivation

Comprehension of biological effects
caused by ion irradiation

Comprehension of different effectiveness
caused by different ion types

Outline

Dosimetry considerations: energy deposition and estimation of DNA-damages

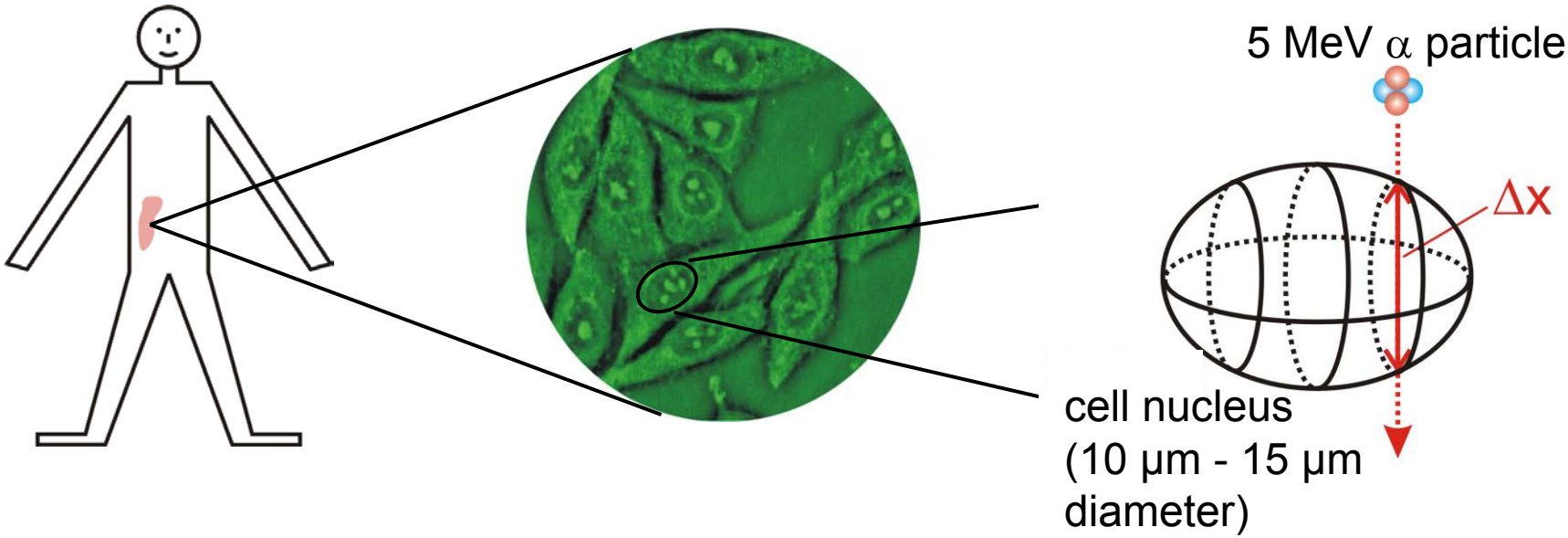
Microdosimetry: comparison of different ion tracks

Microscopic view:
ion track + DNA structure inside the cell nucleus

(one) Experimental approach:
immunofluorescence studies

Dosimetry considerations

Energy deposition in (microscopic) target structures by ion tracks:

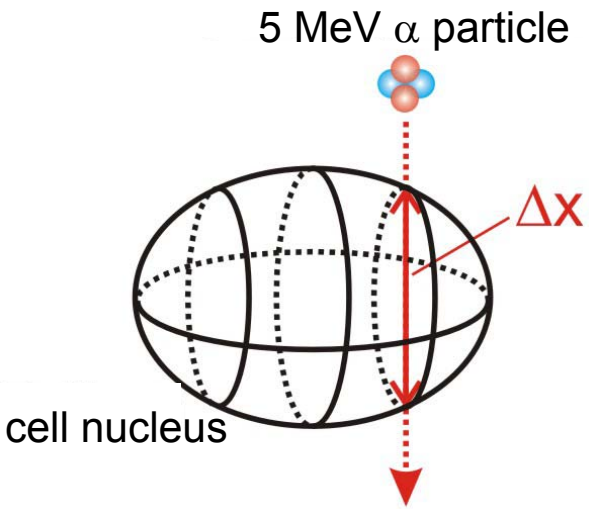


The cell nucleus as container of the DNA-molecule is the essential target structure for ionising radiation.

For HeLa – cell nuclei:

$V_{\text{cell nucleus}} \approx 710\ \mu m^3 \Rightarrow m_{\text{cell nucleus}} \approx 0.71\ ng \quad (\rho_{\text{cell nucleus}} = 1\ g/cm^3)$

Dosimetry considerations



Energy deposition $\Delta E = \Delta x \bullet LET$

(LET = linear energy transfer)

Energy dose $ED = \Delta E / m_{cell\ nucleus}$

$\Delta x = 7.6\ \mu m$ and $LET_{5MeV\text{-}\alpha} = 100\ keV / \mu m$

$\longrightarrow ED = 0.17\ Gy$

Each type of ion radiation has a certain LET value.

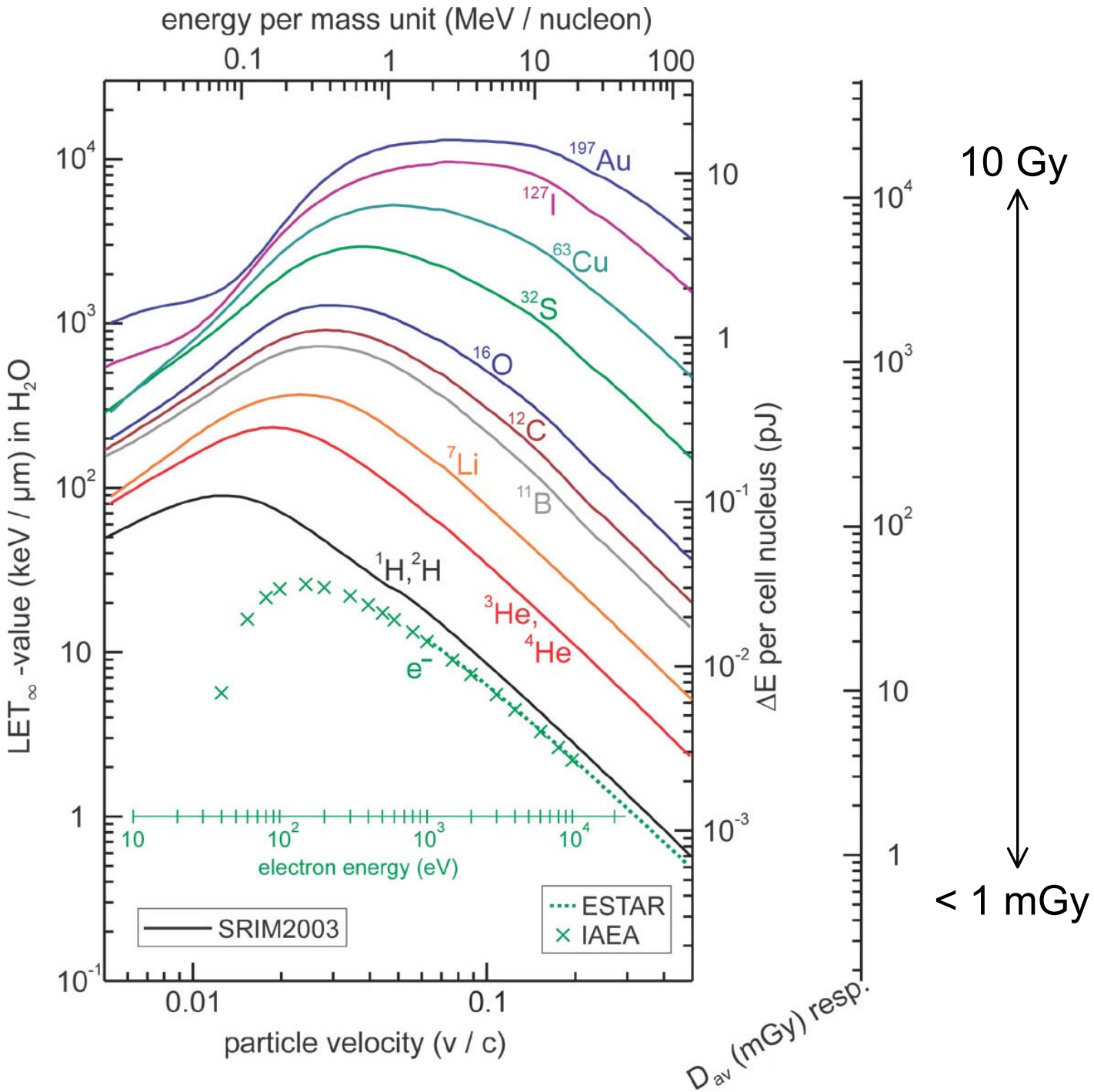
LET values

2 parameters:

Ion atomic Number Z

+

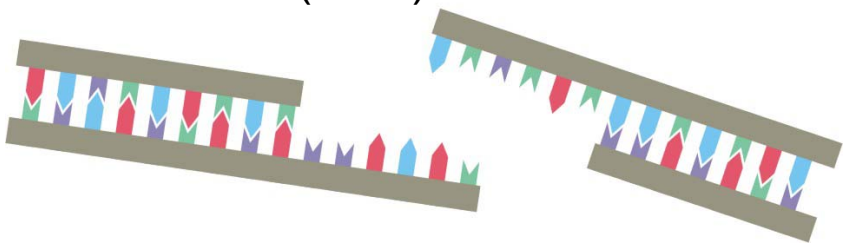
Ion velocity



Estimation of DNA-damages

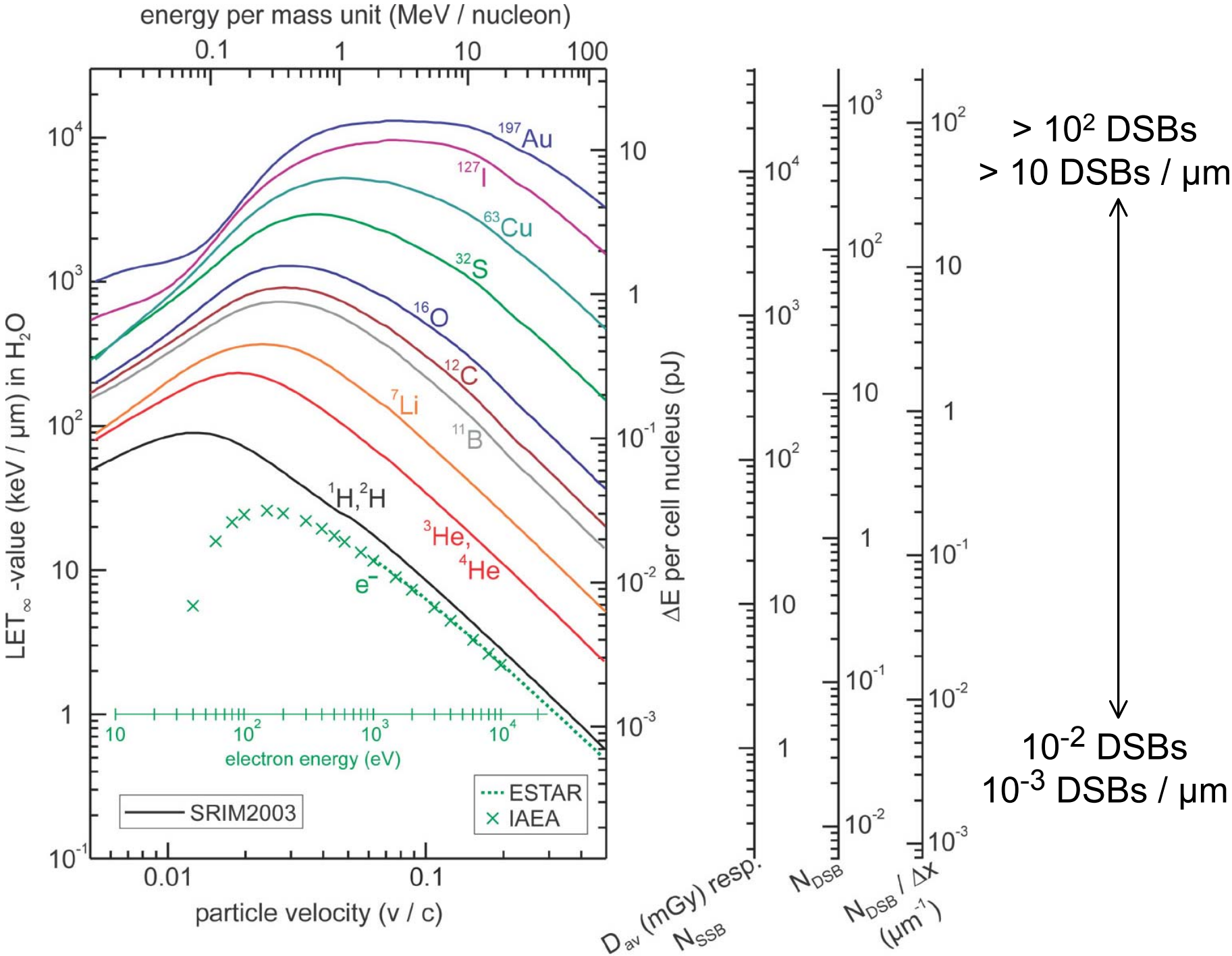
DNA single-strand break (SSB)

DNA double-strand break (DSB)

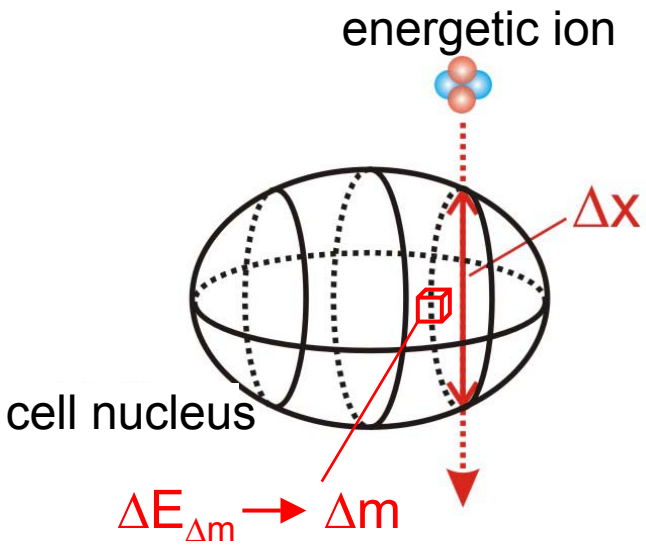


Sparsely ionising radiation:

1000 single-strand breaks (SSBs) per Gy
35 double-strand breaks (DSBs) per Gy


energy per mass unit (MeV / nucleon)
0.1
1
10
100
LET∞ -value (keV / µm) in H2O
ΔE per cell nucleus (pJ)
197Au
127I
63Cu
32S
16O
12C
7Li
11B
1H,2H
3He,
4He
e-
10
10^2
10^3
10^4
electron energy (eV)
SRIM2003
ESTAR
IAEA
0.01
0.1
particle velocity (v / c)
Dav (mGy) resp.
NSSB
NDSB
NDSB / Δx
(µm-1)
> 10^2 DSBs
> 10 DSBs / µm
10^-2 DSBs
10^-3 DSBs / µm

Micro dosimetry



Energy deposition and **average** energy dose can be calculate using the LET.

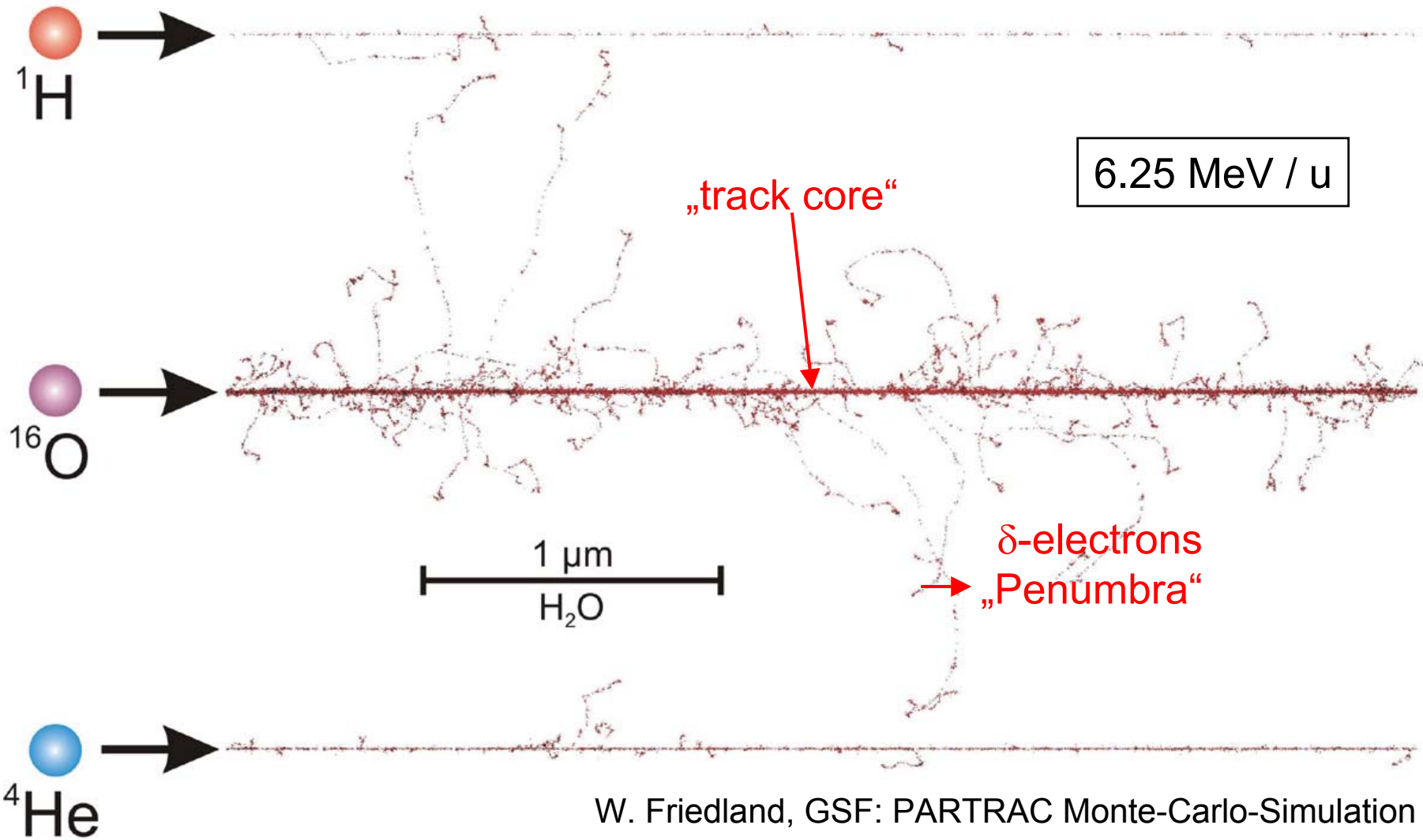
BUT:
Bigger part of the cell nucleus is not affected by deposited energy.

Way out: changeover to local dose $ED_{local}(\vec{r})$

$$ED = \Delta E / m_{\text{cell nucleus}} \longrightarrow \Delta E_{\Delta m} / \Delta m \longrightarrow dE / dm = ED_{lokal}(\vec{r})$$

Energy deposition in ion tracks

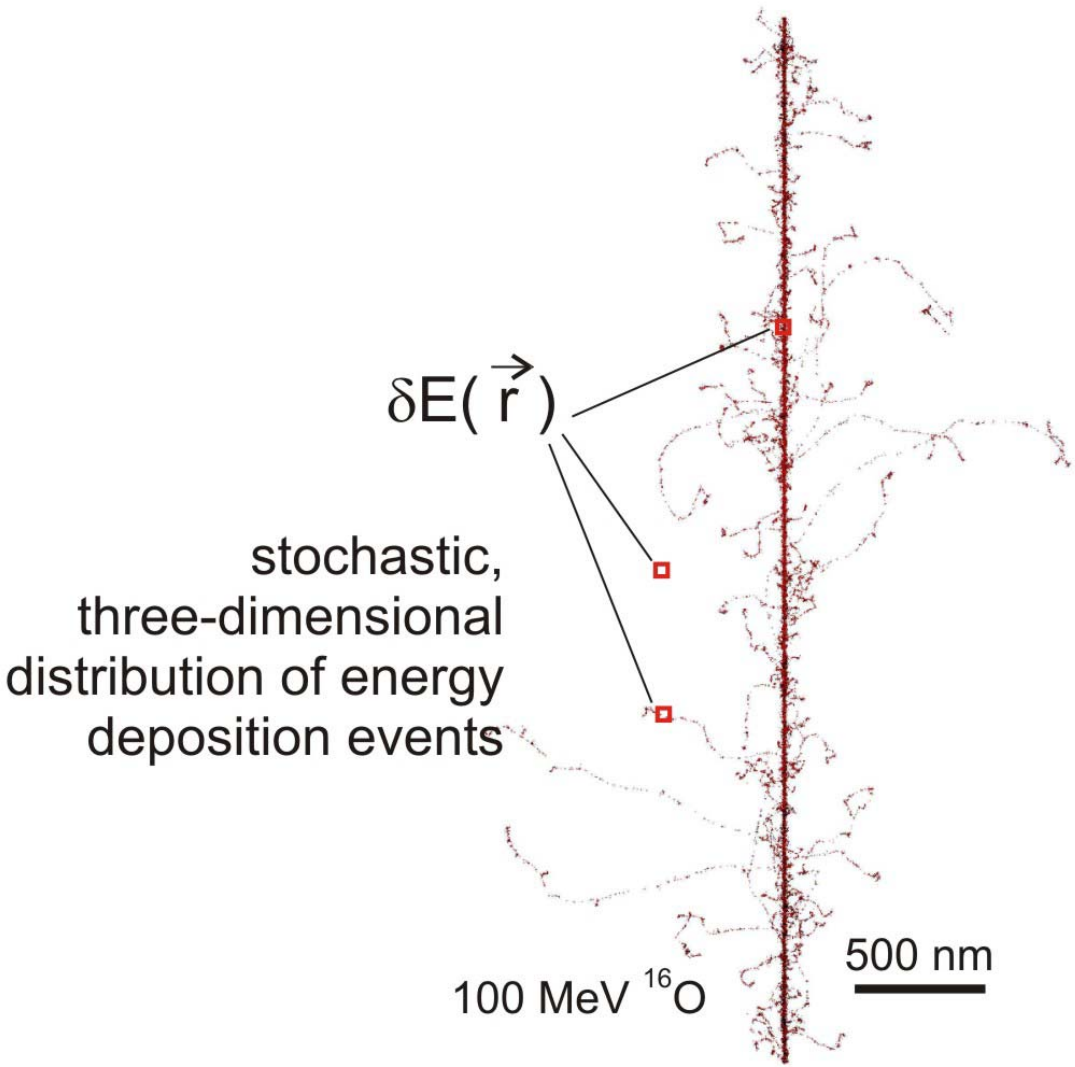
ionisation- and excitation-processes on target molecules
Sparsely and densely damaging ion tracks



W. Friedland, GSF: PARTRAC Monte-Carlo-Simulation

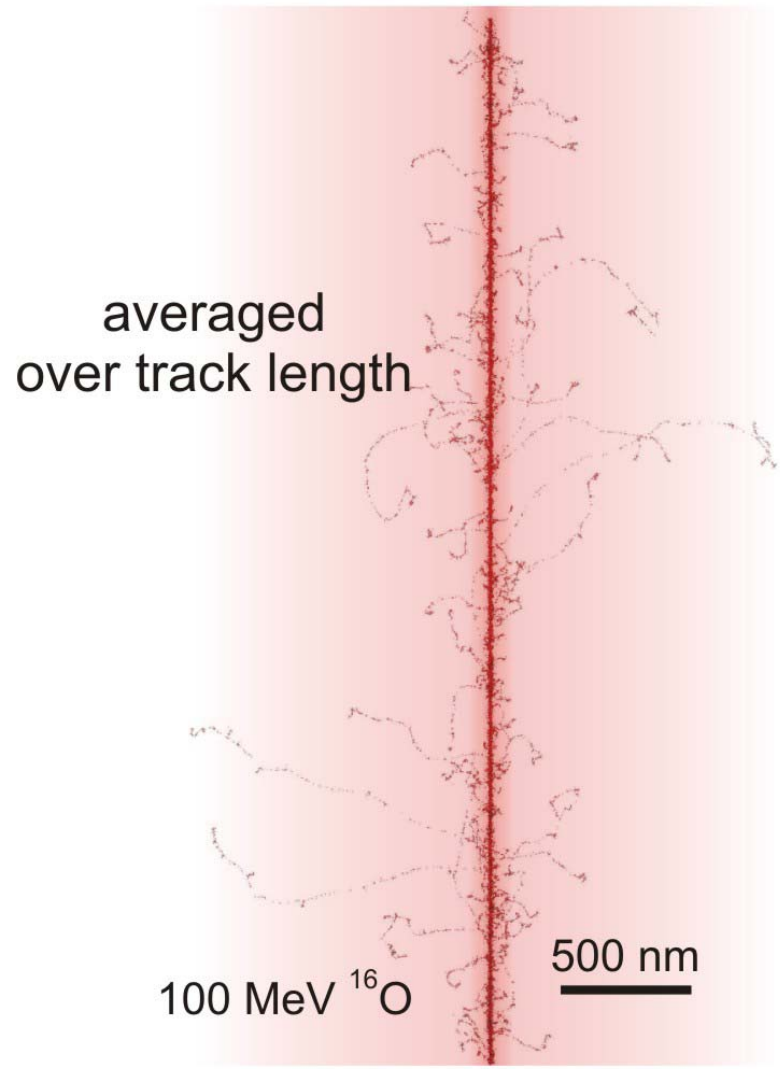
Micro dosimetry

averaged radial dose distribution in H_2O



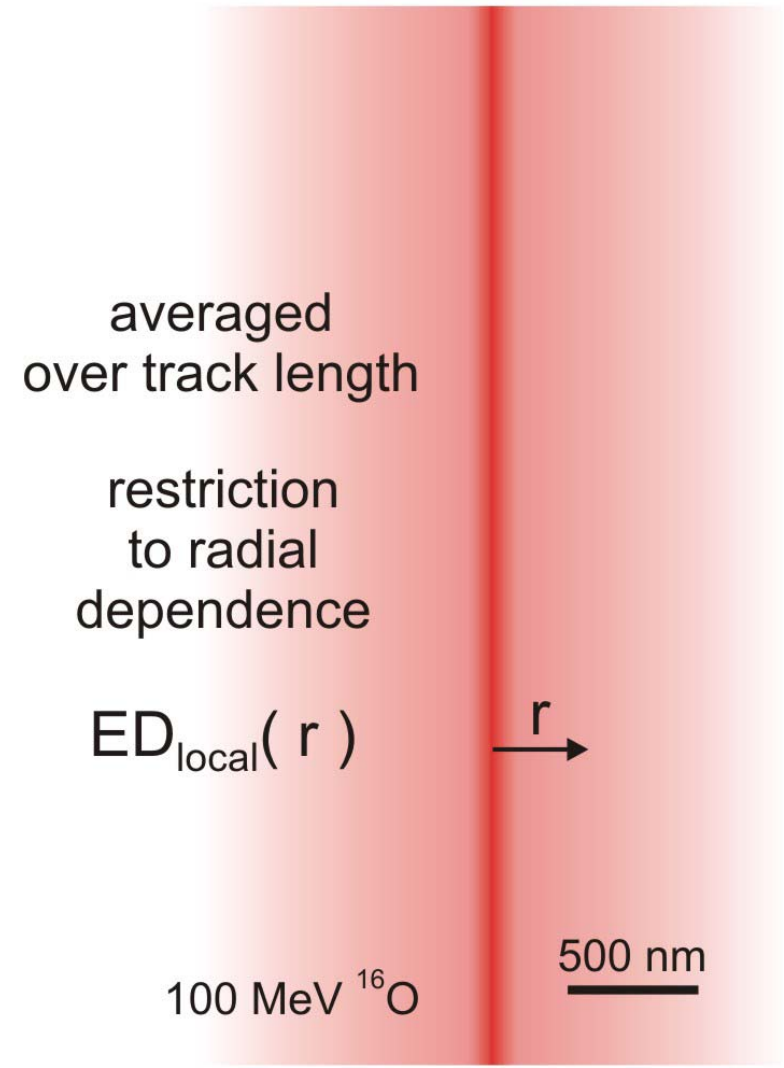
Micro dosimetry

averaged radial dose distribution in H_2O



Micro dosimetry

averaged radial dose distribution in H_2O



Micro dosimetry

averaged radial dose distribution in H_2O

analytical representation fitted to Monte Carlo data in water (Krämer and Kraft, 1994):

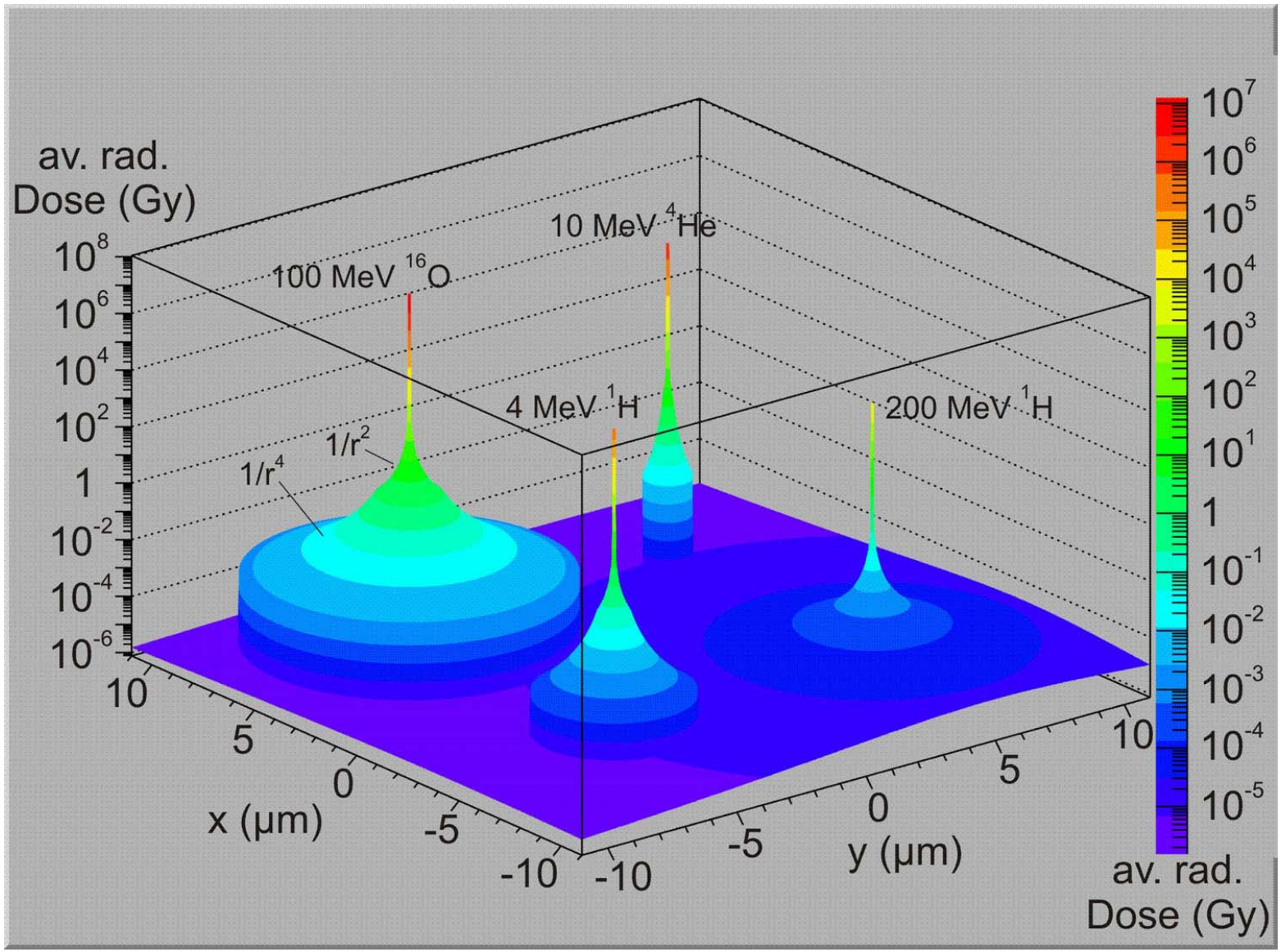
$$ED_{local}(r) = \begin{cases} \dfrac{B}{r} & r \le r_i \\ \dfrac{B \cdot r_i}{r^2} & r_i < r \le r_k \\ \dfrac{B \cdot r_i \cdot r_k^2}{r^4} & r_k < r \le r_{\max} \\ 0 & r > r_{\max} \end{cases}$$

$$r_i = 1\,nm\,, \quad r_k = 45\,nm \cdot (E/A)^{1.75} \propto v^{3.5}\,, \quad r_{\max} = 5 \cdot r_k$$

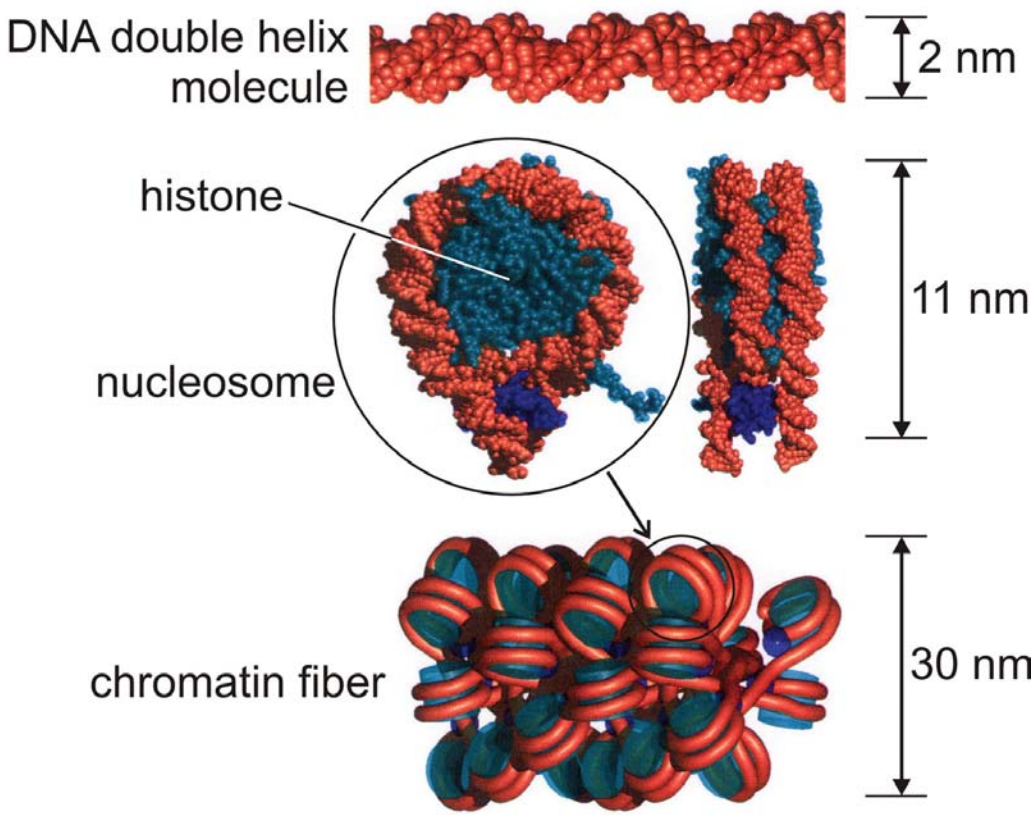
$$B = \frac{1}{\rho_{H_2O}} \cdot LET \cdot \frac{1}{2\pi \cdot r_i \cdot [5.28 + 1.75 \cdot \ln(E/A)]}$$

Micro dosimetry

averaged radial dose distribution in H_2O



Microscopic view: DNA distribution in the cell nucleus

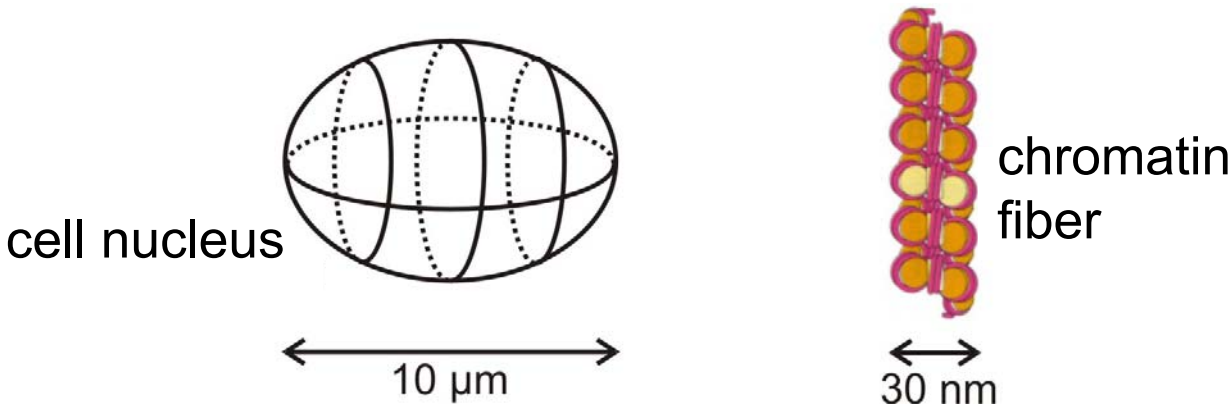


Ph. Bernhardt, PhD thesis

Total lenght of 30-nm-chromatin fiber in human cell nucleus: 5.5 cm

Microscopic view: DNA distribution in the cell nucleus

Relation cell nucleus ⟷ chromatin



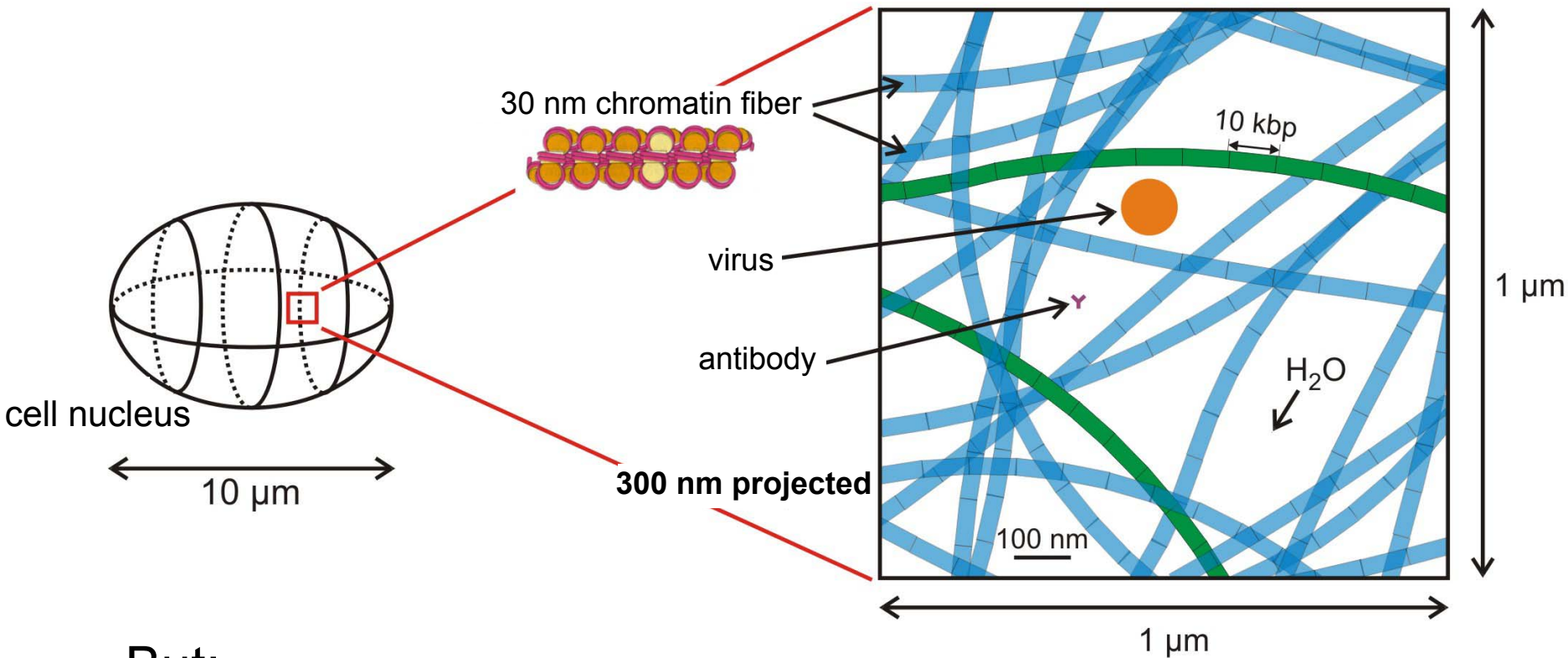
$V_{cell\ nucleus} \approx 710\ \mu m^3$ $V_{chromatin} \approx 39\ \mu m^3$

$V_{chromatin} / V_{cell\ nucleus} = 5.5\ \%$

→ **94.5 % of cell nucleus is not occupied by chromatin.**

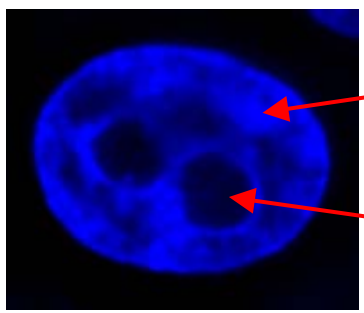
Microscopic view: DNA distribution in the cell nucleus

Assumption: chromatin fibers are distributed homogeneously and randomly inside the cell nucleus

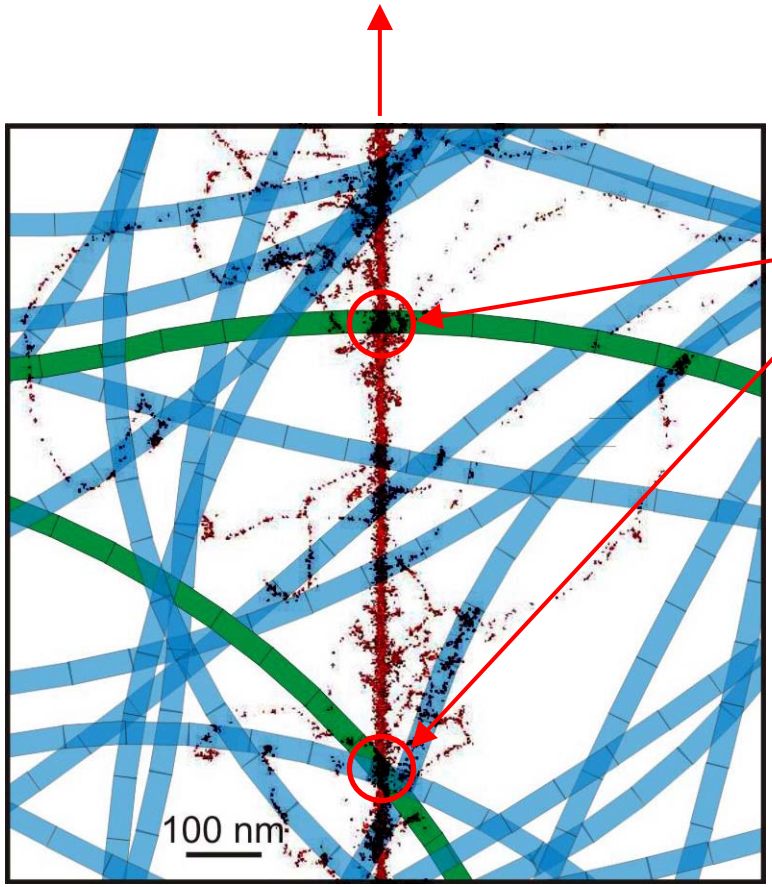


But:

DAPI-image of cell nucleus



Interaction: ion track — cell nucleus



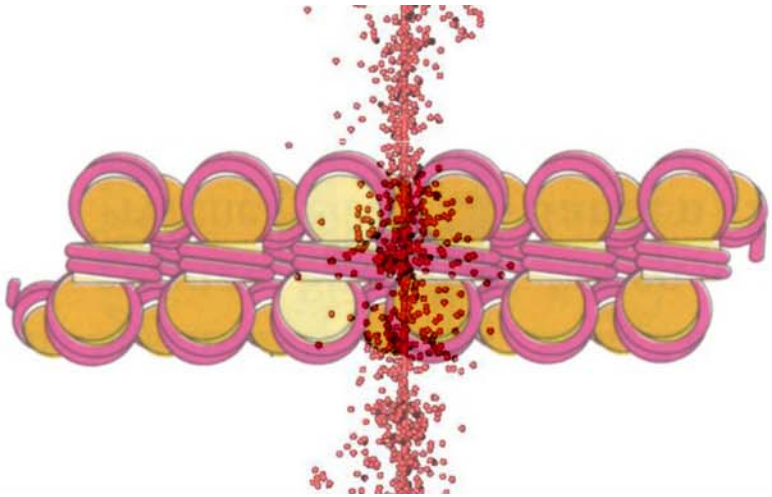
Direct ion hits in chromatin fibers

→ **Direct effects**

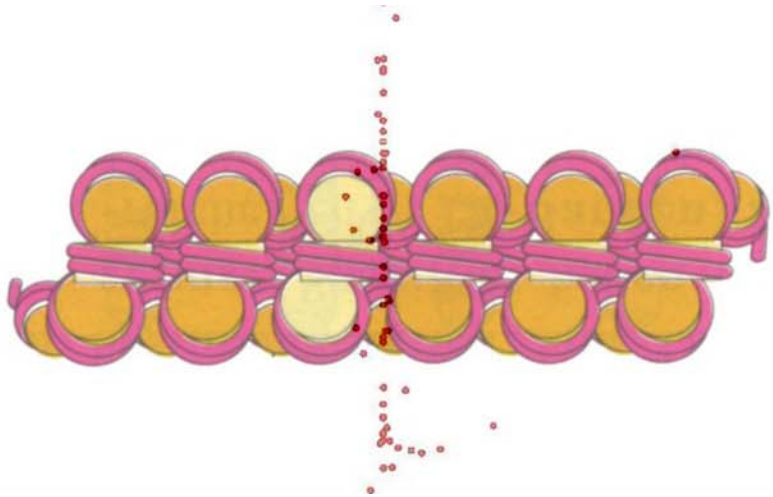
100 MeV ^{16}O

Microscopic view

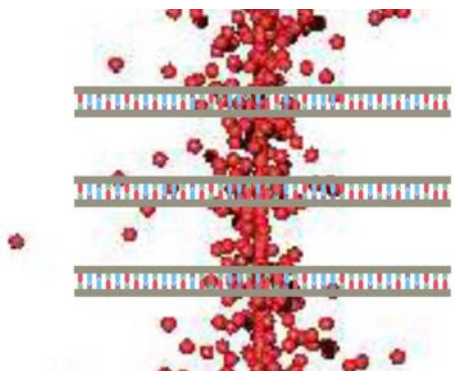
Direct effects:

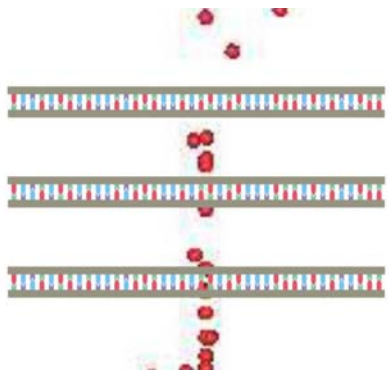


densely ionising



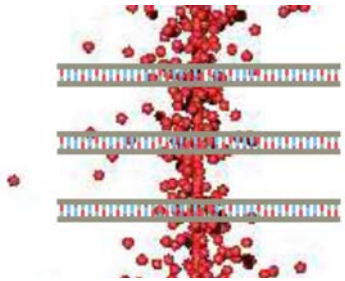
sparsely ionising



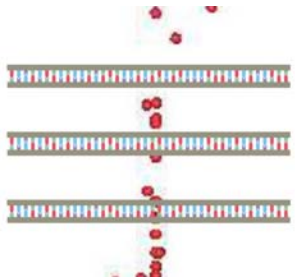


Microscopic view

densely ionising

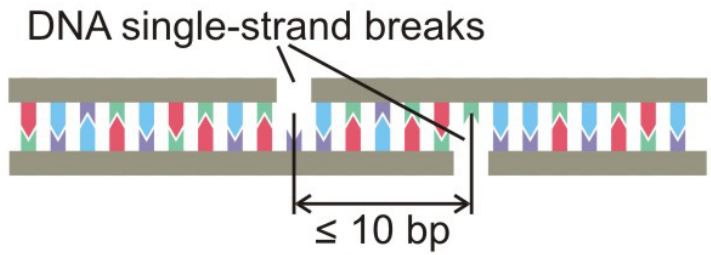


sparsely ionising

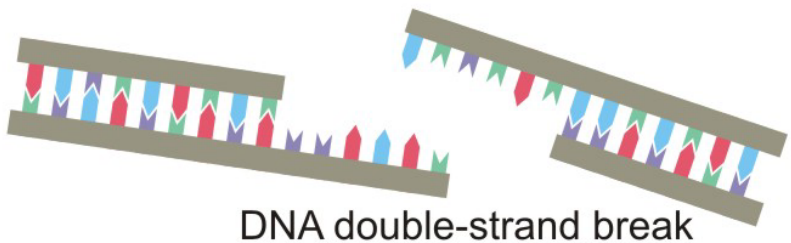


DNA double-strand breaks emanate from neighboured DNA single-strand breaks

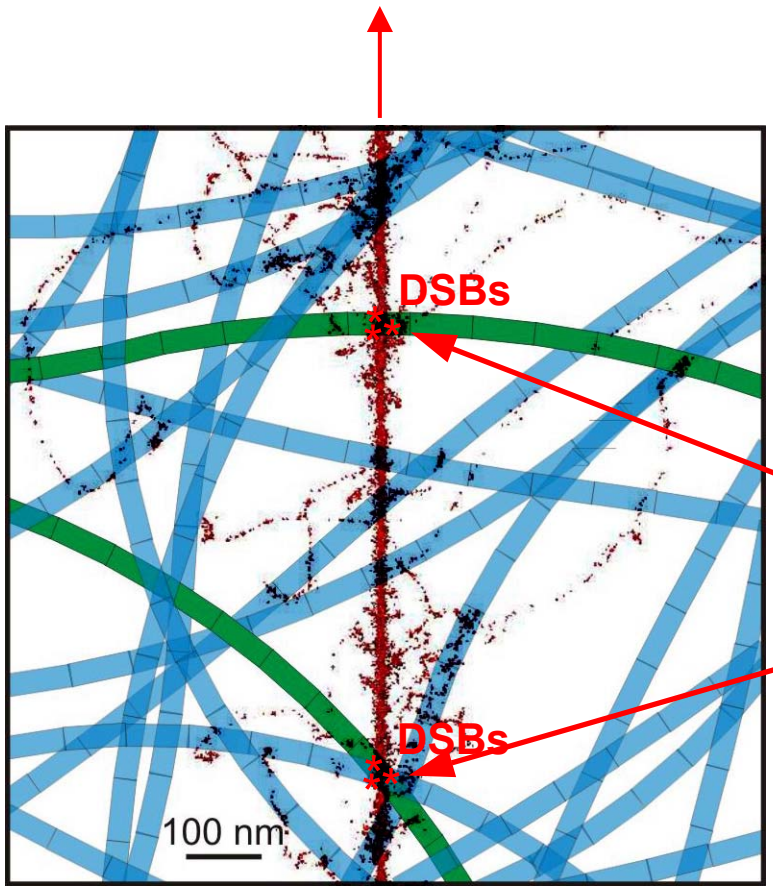
Densely ionising (high LET) irradiation generates a disproportionate number of double-strand breaks



DNA double-strand breaks are the most serious DNA damages.



Microscopic view

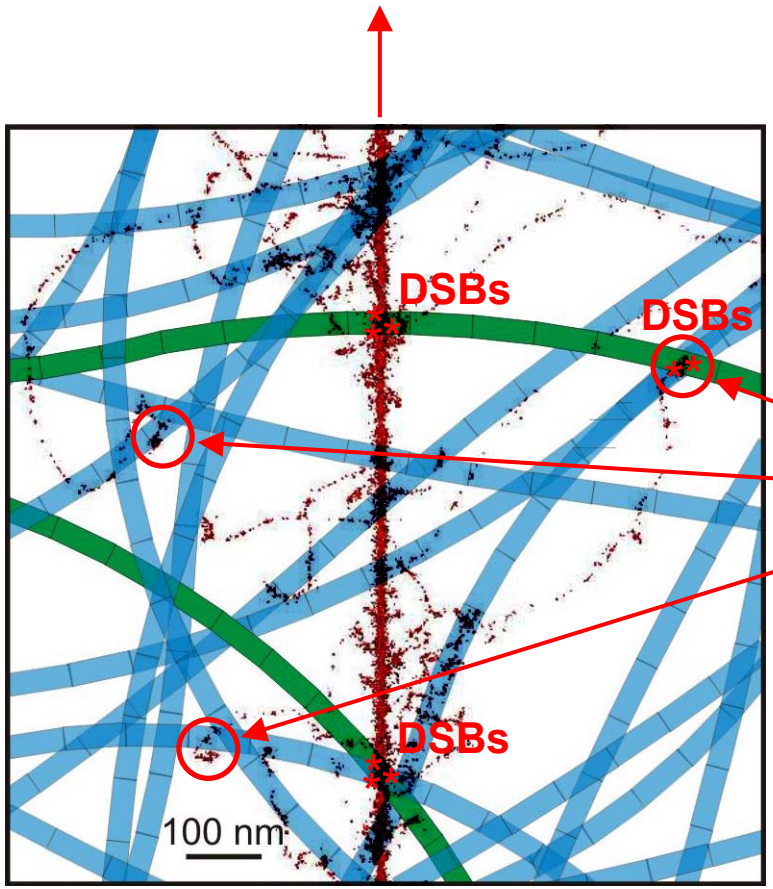


100 MeV ^{16}O

For heavy ion tracks:
clustered DNA-DSBs
near the track center
→ High biological
effectiveness

Microscopic view

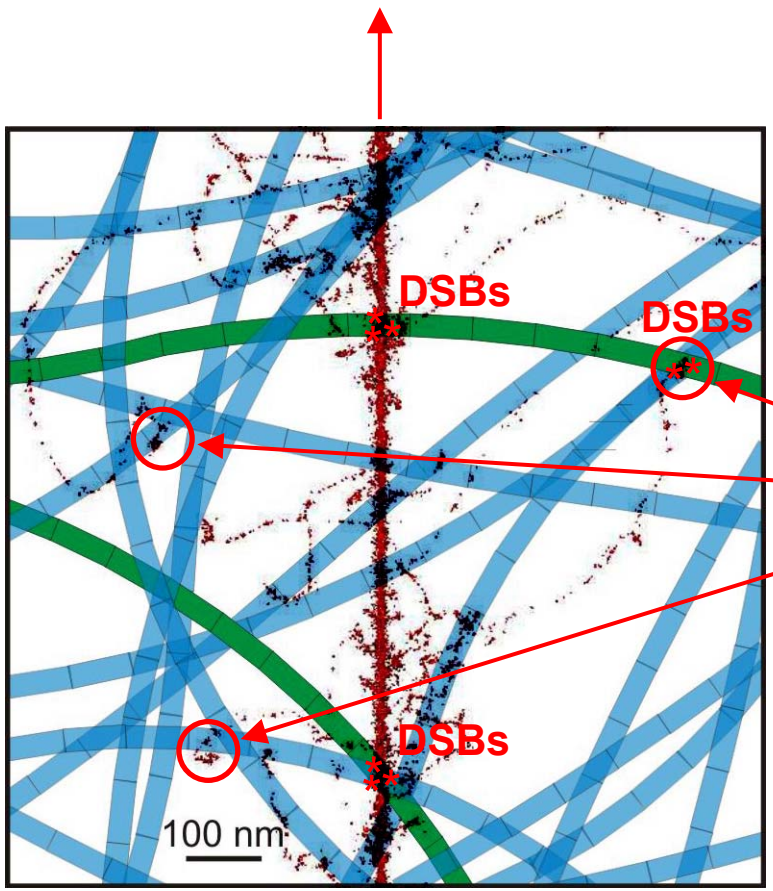
Damaging action by secondary electrons:

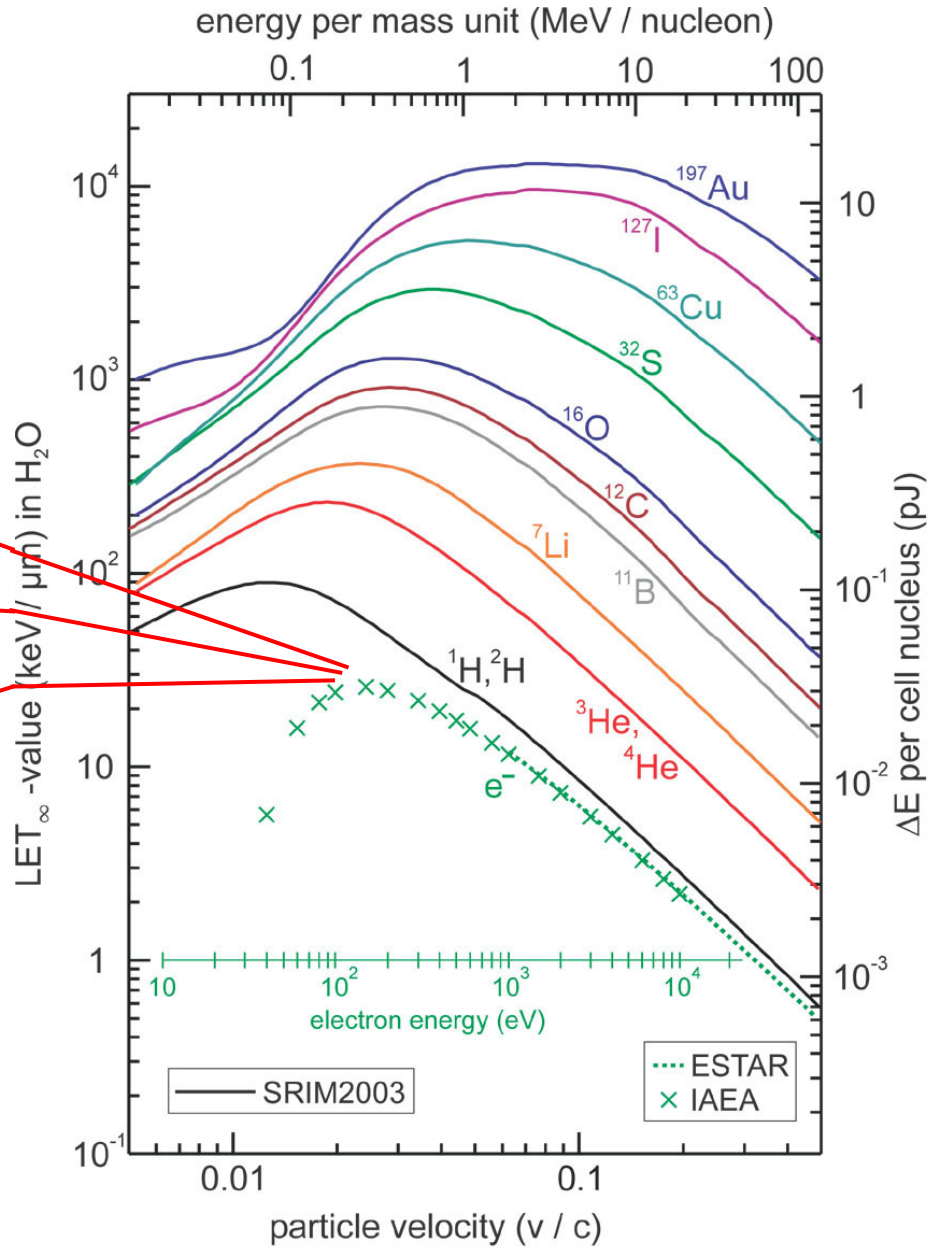


At the end of secondary electron tracks sites of high damage density occur.

100 MeV ^{16}O

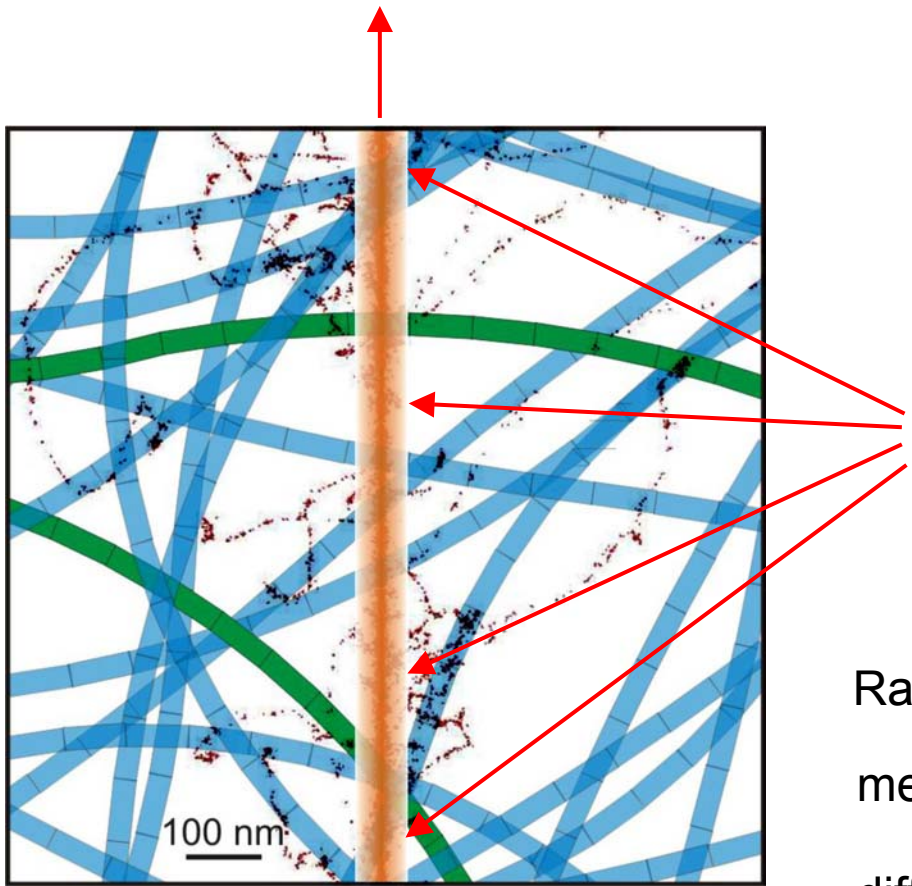
Microscopic view





Microscopic view

Generation of H_2O radicals in the interchromatin space: ⟶ indirect effects



H_2O radicals along the ion track

Range of OH* -radical in the cell nucleus:

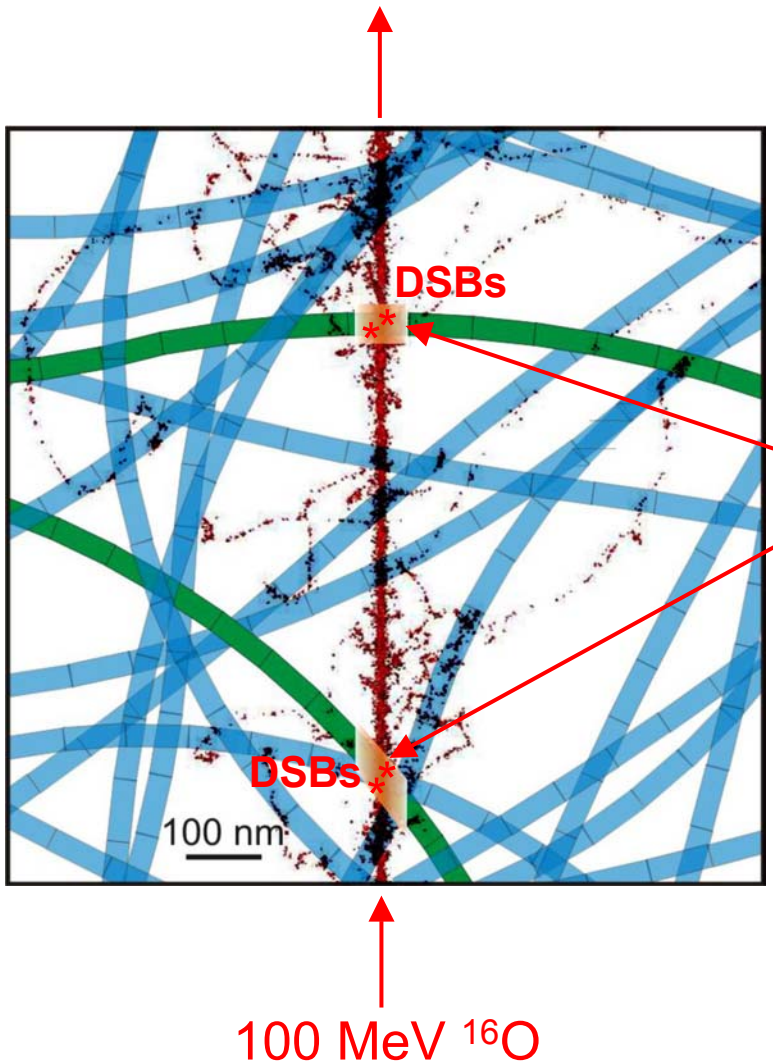
mean life time $\tau_{OH} = 2.5 * 10^{-9}$ s

diffusion constant $D_{OH} = 2.8 * 10^{-9}$ m^2s^{-1}

→ mean diffusion length $\lambda_{OH} = (6*D_{OH}*\tau_{OH})^{0.5} = 6.5$ nm

Microscopic view

Damaging range of OH* - radicals:



Only those OH* - radicals generated in an approx. 10 nm radius around chromatin fibers will reach DNA.

→ Damage structure is not altered substantially by chemical effects.

Microscopic view

Monte-Carlo-Simulation: particle track + cell nucleus architecture

→ prediction of DNA damages (SSBs , DSBs) and their location

e.g. PARTRAC Monte-Carlo-Simulation
W. Friedland, H.G. Paretzke GSF

Experimental Studies: Ion tracks in cell nuclei

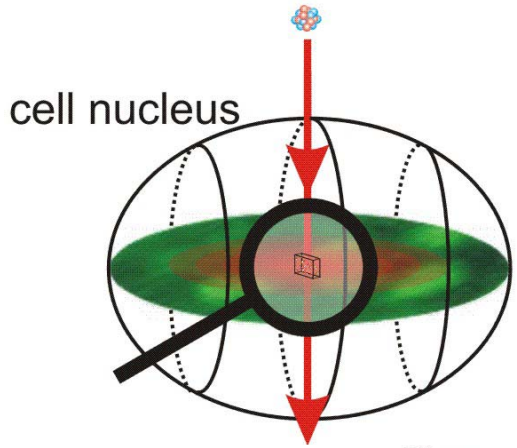
Beams of ions with MeV - energies

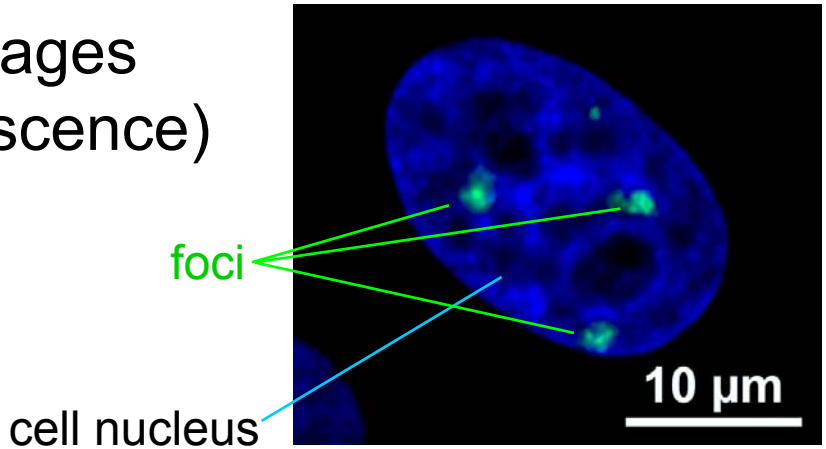
α particles from radioactive sources

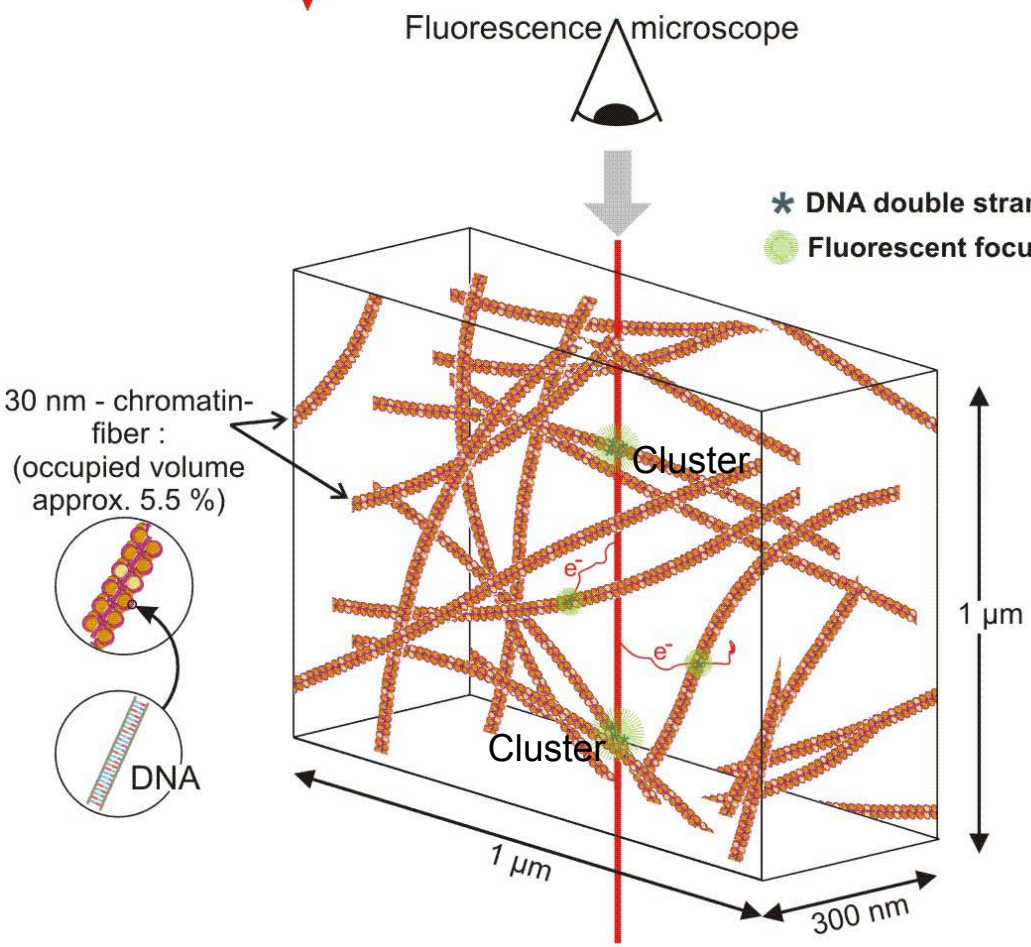
(e.g. ^{241}Am)

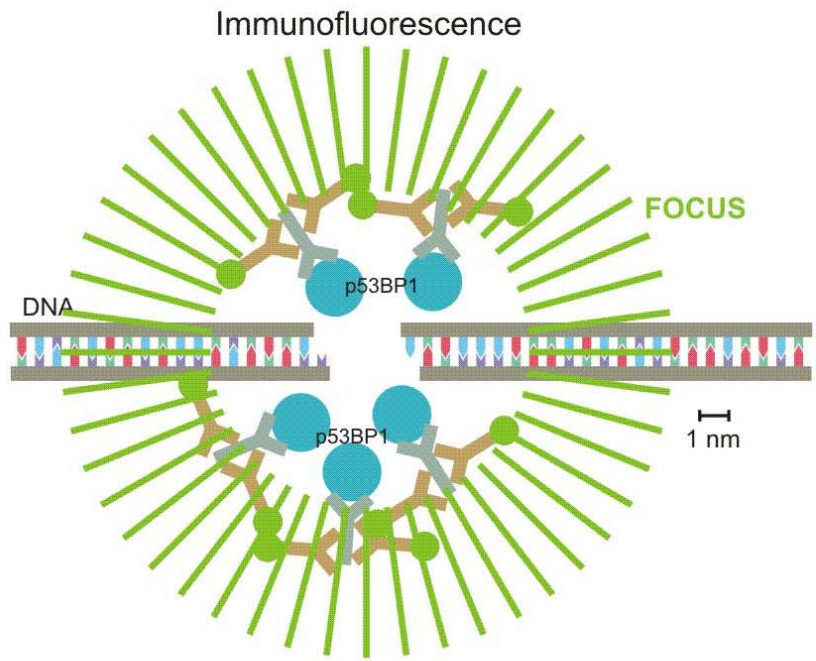
accelerator

Optical observation of DNA-damages (Immunofluorescence)

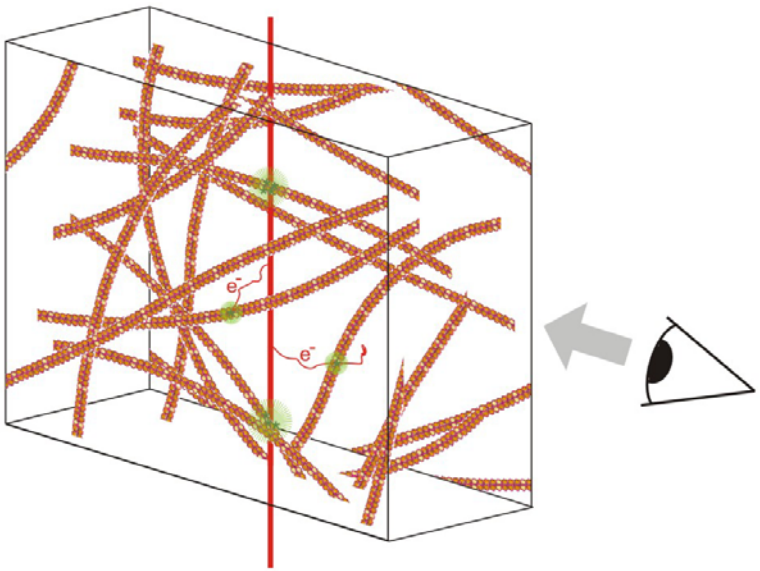




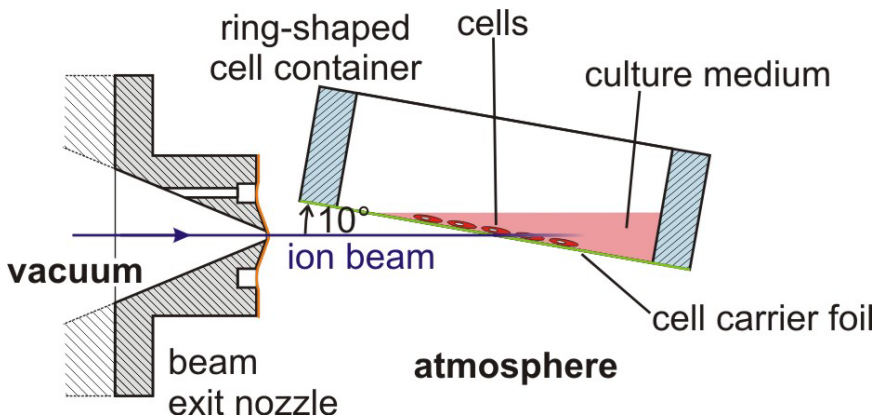


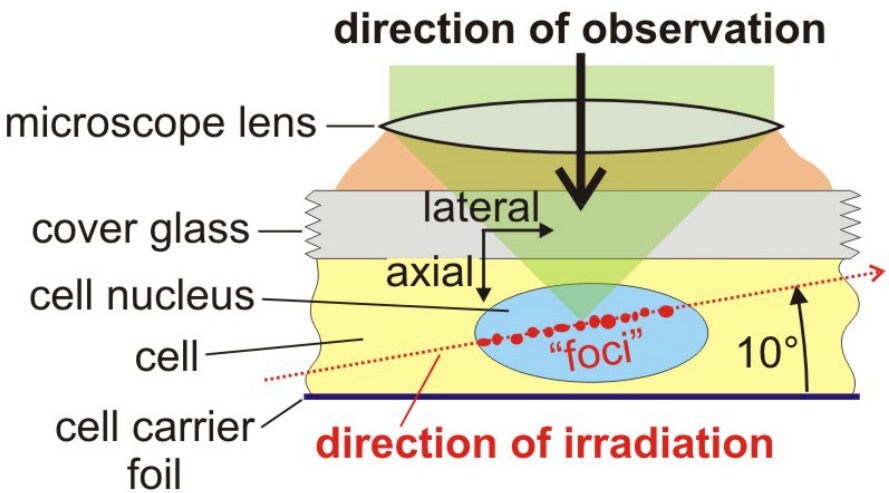


High resolution DSB observation along ion tracks



Irradiation geometry

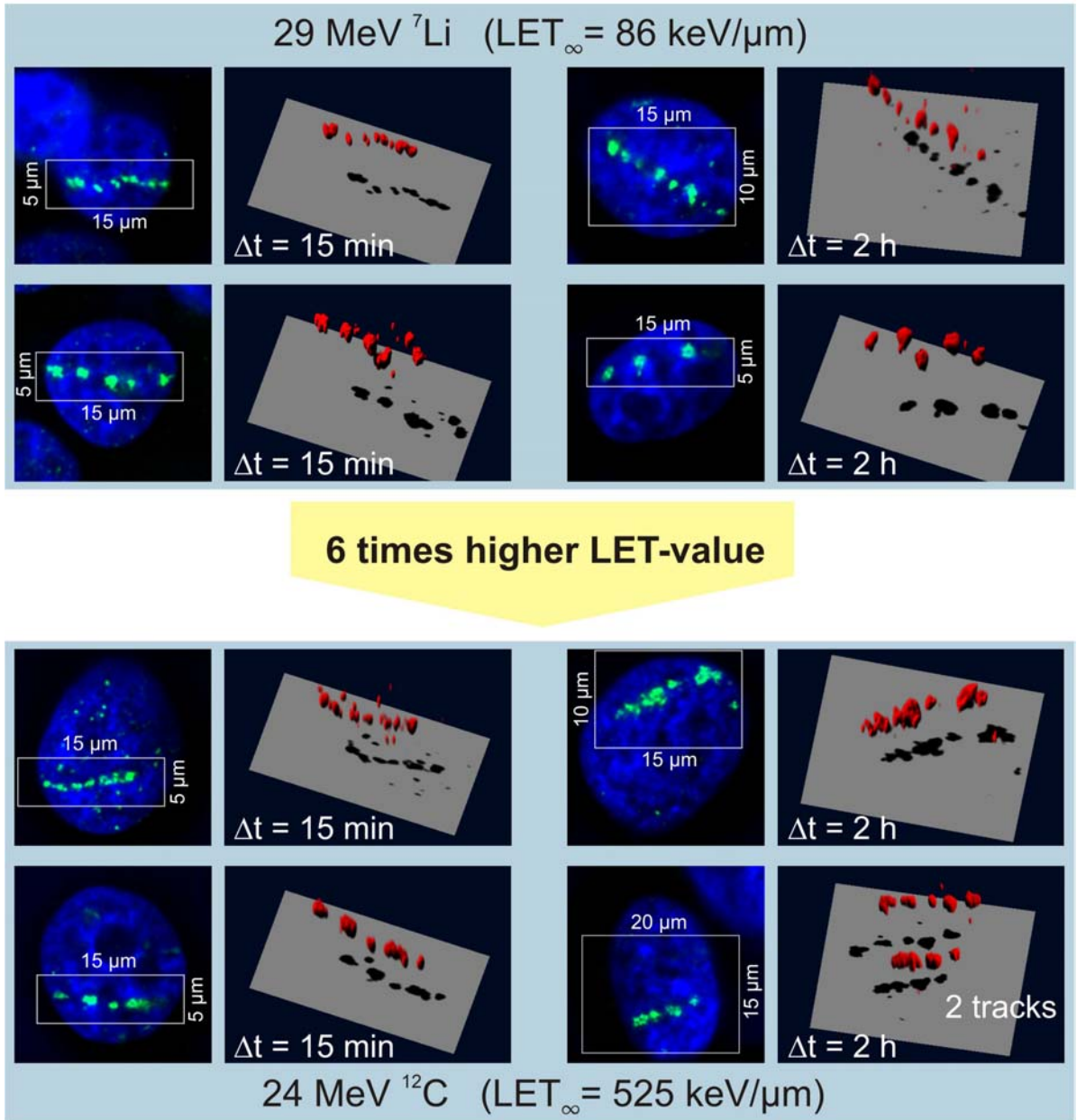




Jakob et al.,
Radiation Research **159**, 676-684 (2003)

Aten et al.,
Science **303**, 92-95 (2004)

Experimental results



< 1 foci per µm
from experiment for
both beam qualities

→ Damage structure seems to be saturated.

→ Number of foci is less than expected.

Hauptner et al.,
Radiation Protection Dosimetry **122**, 147-149 (2006)

Summary

Damaging action from ion tracks:
particle track + cell nucleus architecture

simpler approximations using
(micro) dosimetry considerations

immunofluorescence techniques
show track structure in the cell nucleus
after ion irradiation

"Spatial Distribution of DNA Double-Strand Breaks from Ion Tracks"
http://www.e12.physik.tu-muenchen.de/groups/rim/papers/hauptner-mfm-2.pdf

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S. Dietzel, H. Strickfaden, T. Cremer
LMU München, Department Biologie II

W. Friedland, H.G. Paretzke
GSF, Institut für Strahlenschutz

"Spatial Distribution of DNA Double-Strand Breaks from Ion Tracks"
http://www.e12.physik.tu-muenchen.de/groups/rim/papers/hauptner-mfm-2.pdf