From Radiobiology to Radiation Therapy: Action of Heavy Charged Particles in Biological Material

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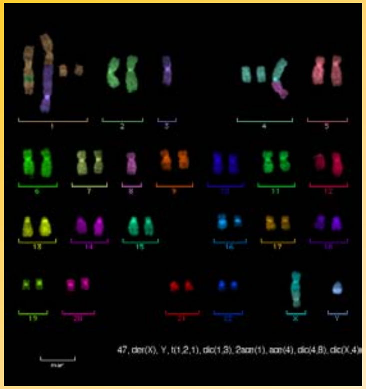

Challenges of biophysical research with heavy ions

- **Mechanisms of biological damage induced by densely ionizing radiation: cellular response, signal transduction, genetic mutation**
- **Charged-particle cancer therapy**
- **Radiation protection in long-term space missions**

*****Bevelac (Berkeley), GSI (Darmstadt), HIMAC (Chiba), AGS-BNL (Brookhaven)**

Radiobiological effects of highly charged ions

- **High and low LET radiations act differently on DNA (differing degrees of spatial clustering of ionizations!)**

↓

- **Number and size distribution of DNA fragments show a significant dependence on radiation quality**

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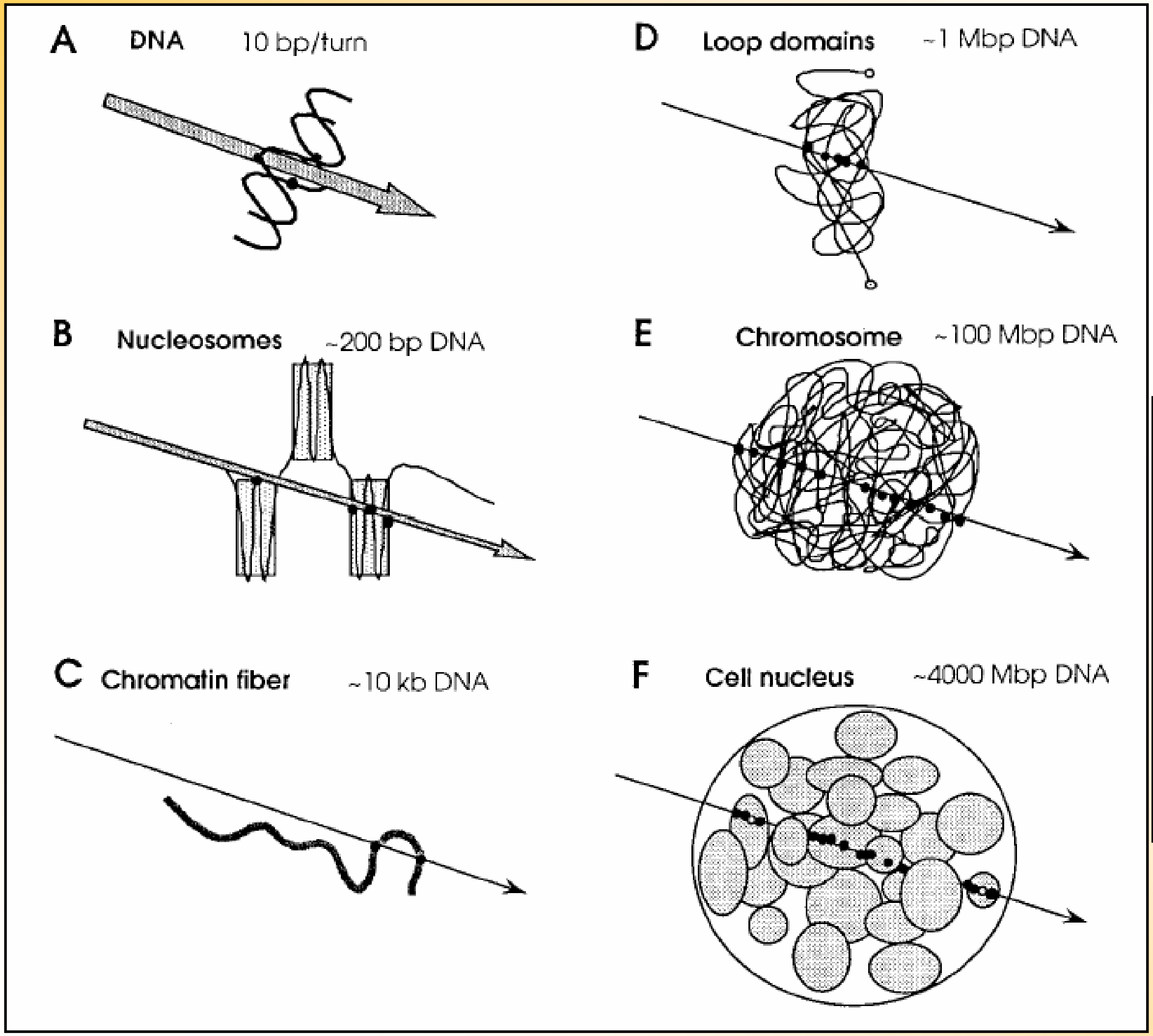
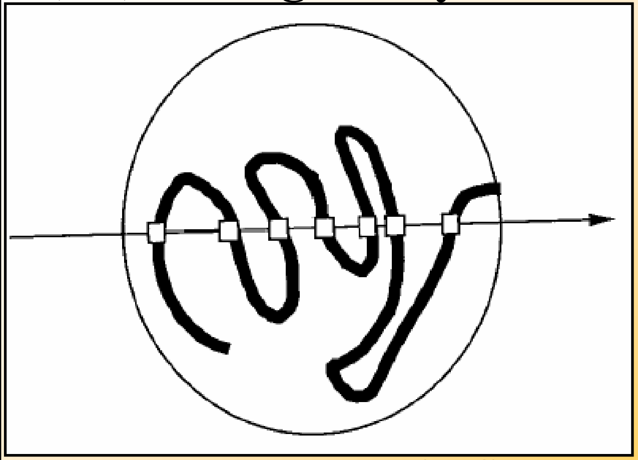
- **The effect can be attributed to the random distribution of radiation tracks and deterministic localisation of energy within the track**

Lesion clustering (multiple damage sites MDS) occurs at various levels of chromatin organization



A: Locally MDS

B, C, D: Regionally MDS

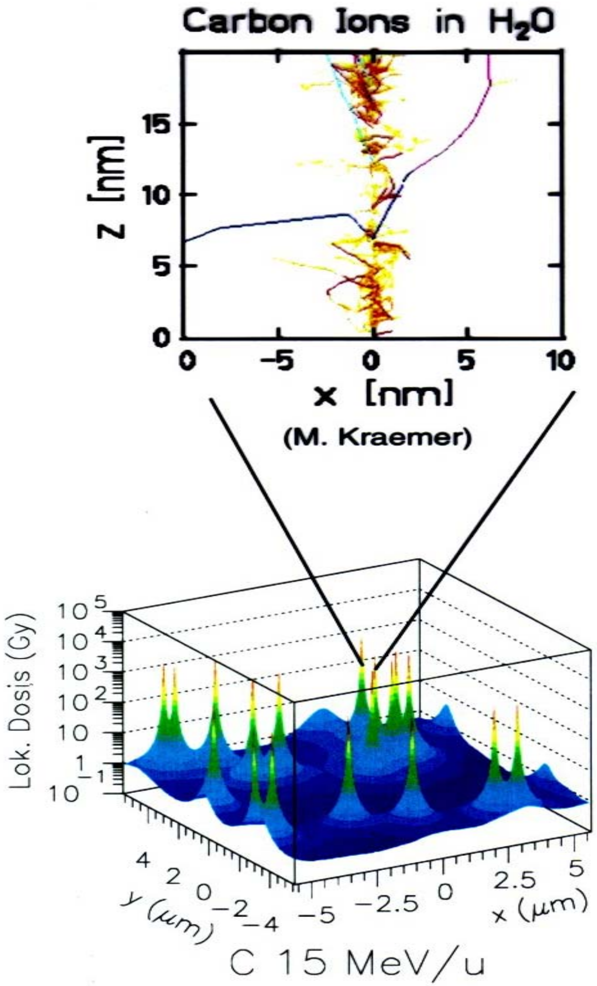


30 nm chromatin fiber

B. Rydberg, Acta Oncol., 2001.

- Krämer, Kraft, *Radiat. Environ. Biophys., (1994)*
- Cucinotta, Nikjoo, Goodhead, *Radiat. Environ. Biophys., (1999)*
- Scholz, Kraft, *Radiat. Protec. Dosim., (1994)*
- *Holley, Chatterjee, Radiat. Res., (1998)*

Physical Characteristics of Ion Beams



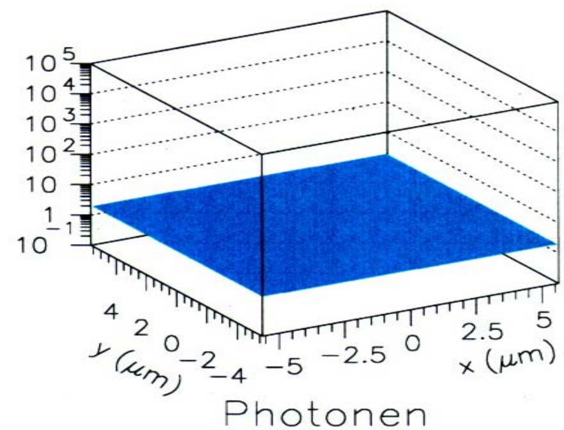
Emission of δ-electrons

Radial Dose Profile:
D(r): Expectation value

$D(r) \sim 1/r^2$

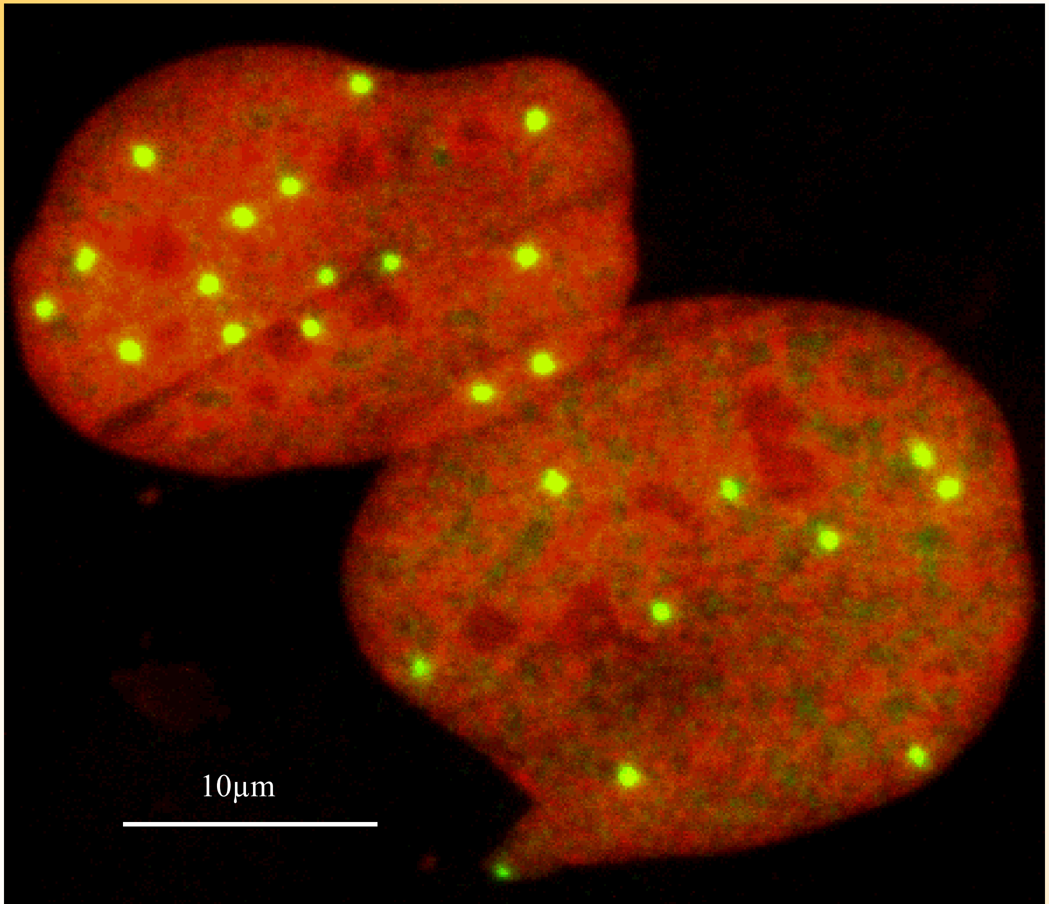
$R_{Track} \sim E^c$

$c \approx 1.7$
(empirical !)



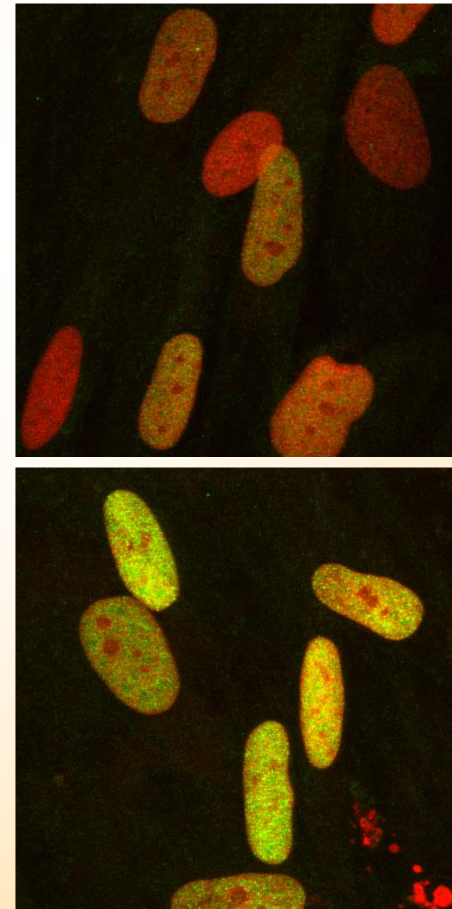
p21 foci in human fibroblast nuclei traversed by Pb ions

^{207}Pb: 3.0 × 10^{6} cm^{-2}



15 min

X-rays: 10 Gy



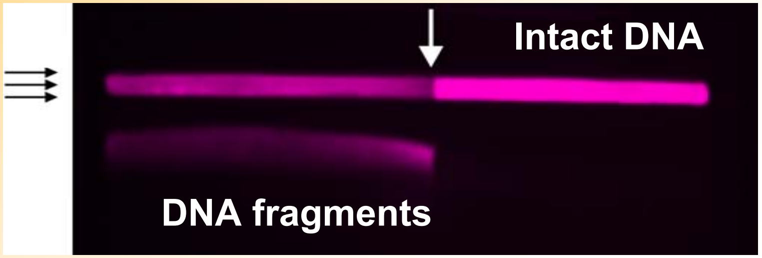
0 h

1.5 h

B. Jakob et al., Radiat Res., 2000.

Intracellular DSB induction and rejoining along the track of carbon particle beams

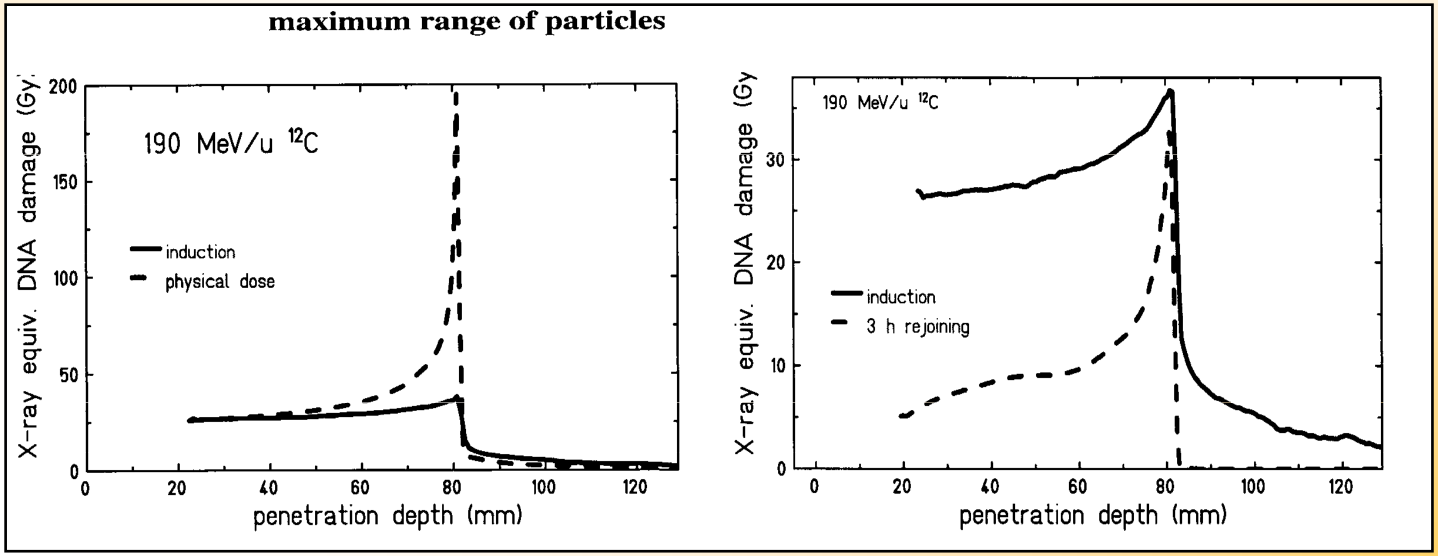
^{12}C
190 MeV/u



LET: determines the frequency and complexity of clustered damage

low LET: 20-30% of DSBs from 2 SSBs

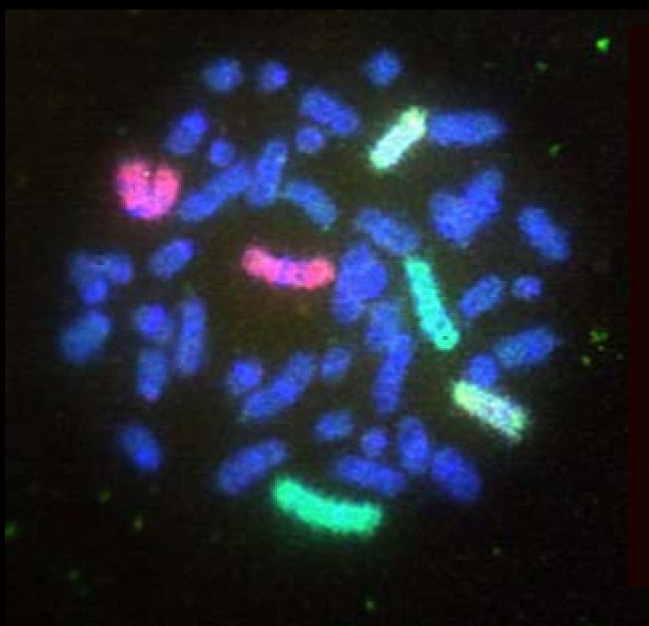
high LET: 80-90% of DSBs from 2 SSBs



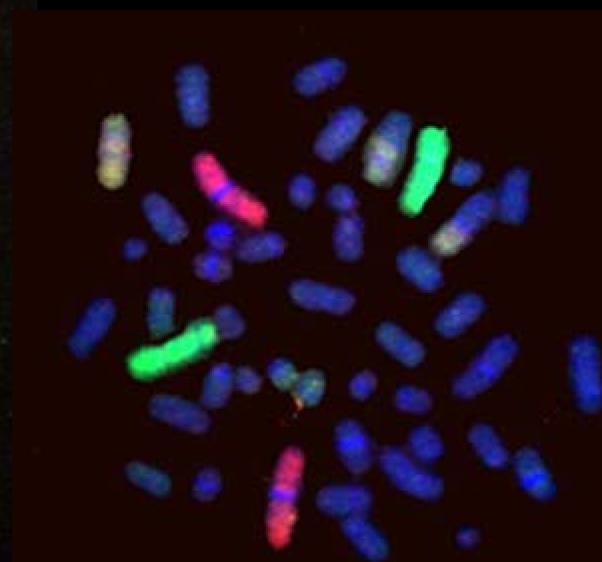
Heilmann J. et al., Int J Radiat Oncol., 1996.

Chromosomal aberrations in blood lymphocytes

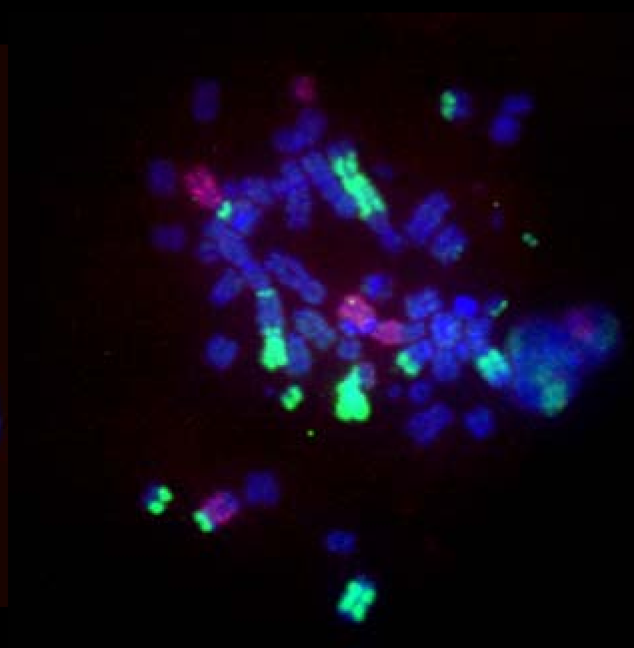
George et al., 2001



Normal



Simple reciprocal exchange involving chromosome 5

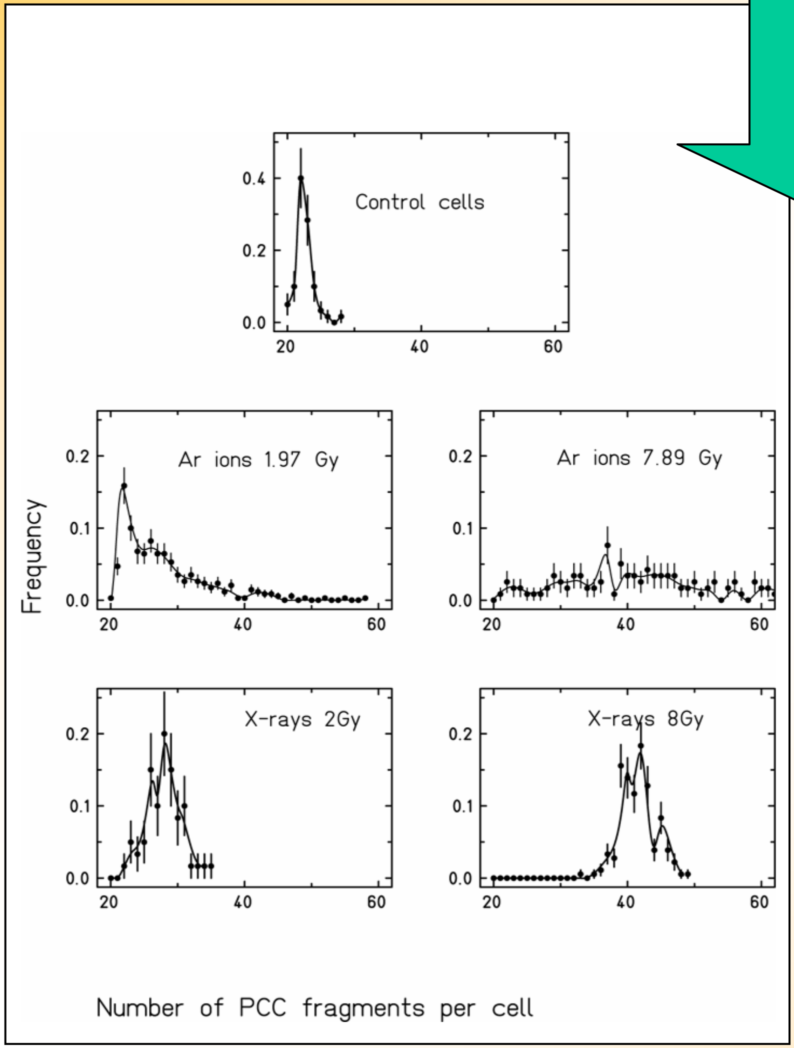


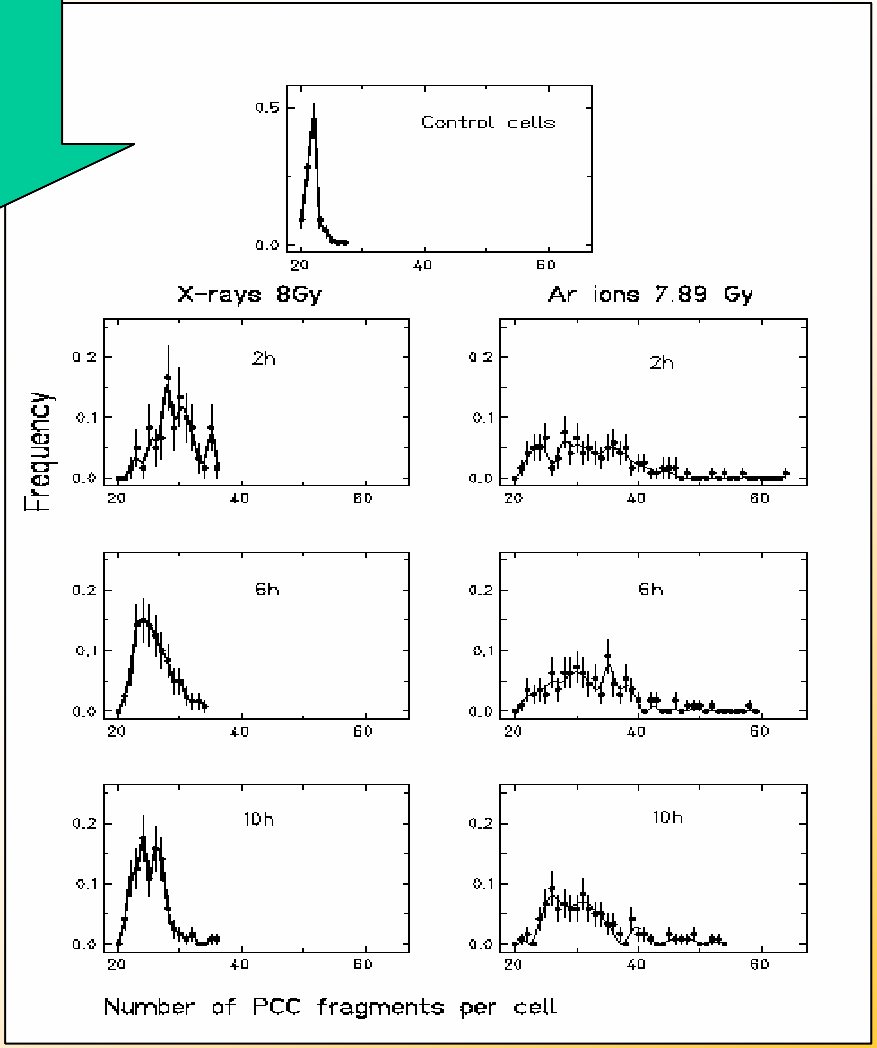
Complex exchanges involving chromosomes 1, 2, and 5

Ritter et al.,

IJRB, 2001

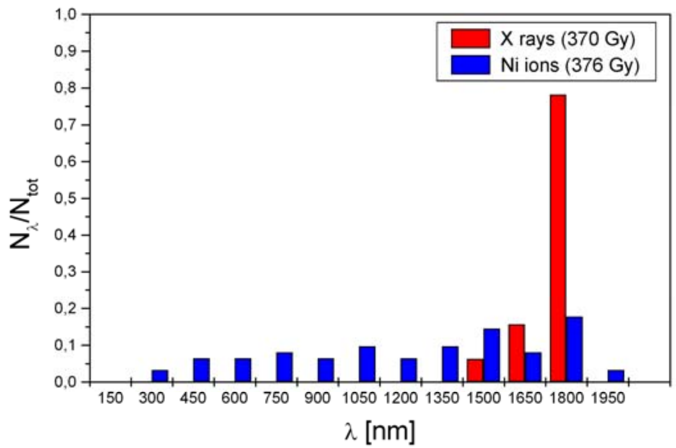
Initial damage and time-dependent repair: X-rays *versus* Ar -ions

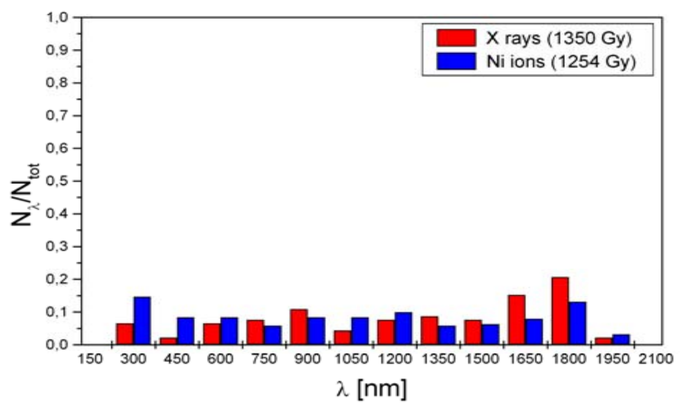


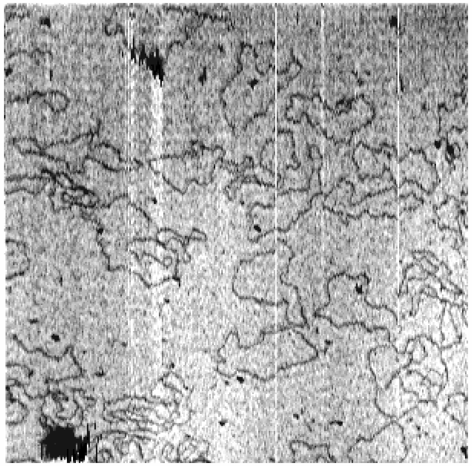


Ni- ions
E=3.5MeV/u, LET=4120 keV/μm

Direct visualisation: AFM measurements

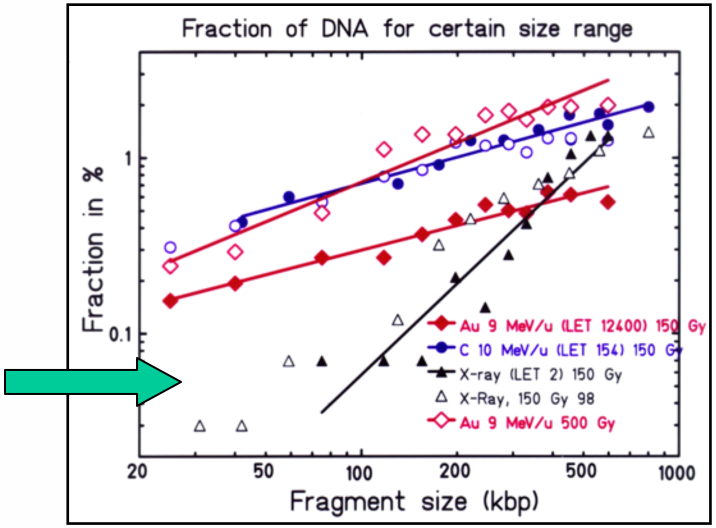






plasmid DNA

ΦX174 (5386 bp)



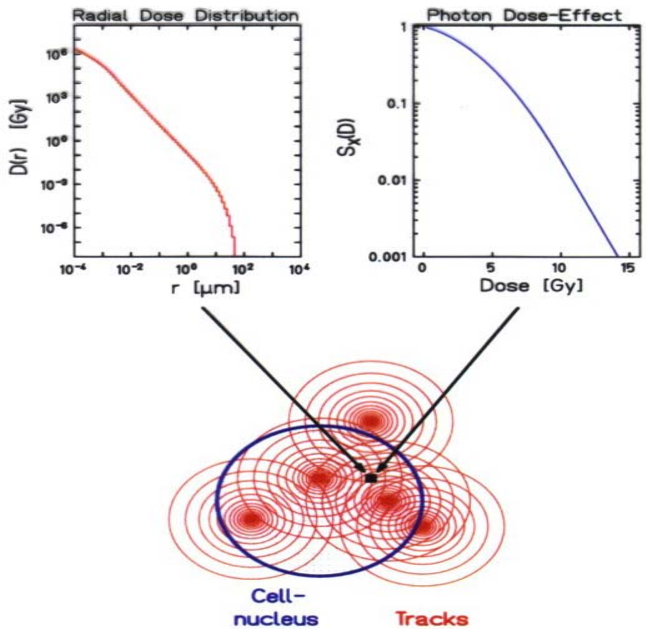
Local Effect Model for Calculation of RBE

Input data:

- Photon dose effect curve
- Radial dose distribution of tracks
- Target size (cell nucleus)

Brons et al.

Radiat. Environ. Biophys., 2003



Microscopic stochastic features of the track:

LEM (Local Effect Model)

$$\overline{N}_{lethal} = \int \frac{-\ln S_X(d(x,y,z))}{V_{Nucleus}} dV_{Nucleus} \Rightarrow S_{Ion} = e^{-\overline{N}_{lethal}}$$

$d(x,y,z)$: local dose

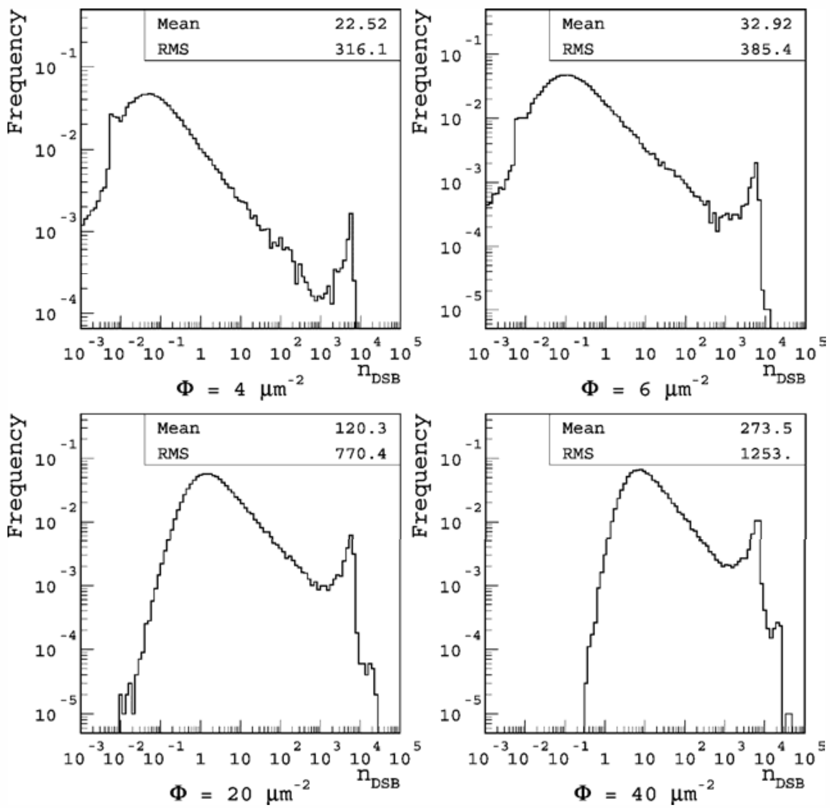
$$\langle n_{DSB} \rangle_{D_i} = -\ln(P_0(D_i))$$

$$P_0(D_i) = 1 - P_{\geq 1}(D_i)$$

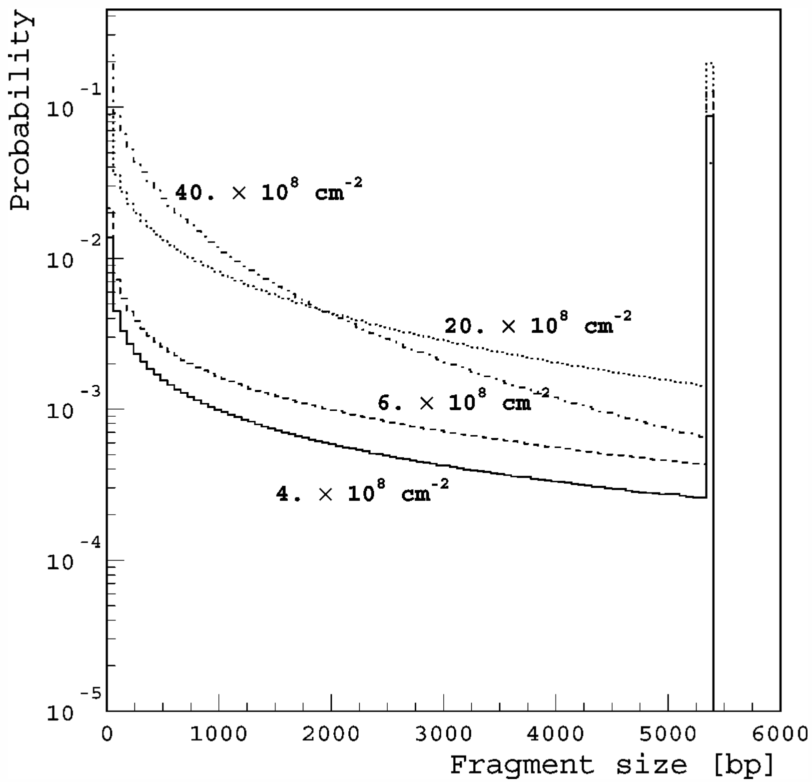
Scholz et al., Rad.Env.Biophys. 1997

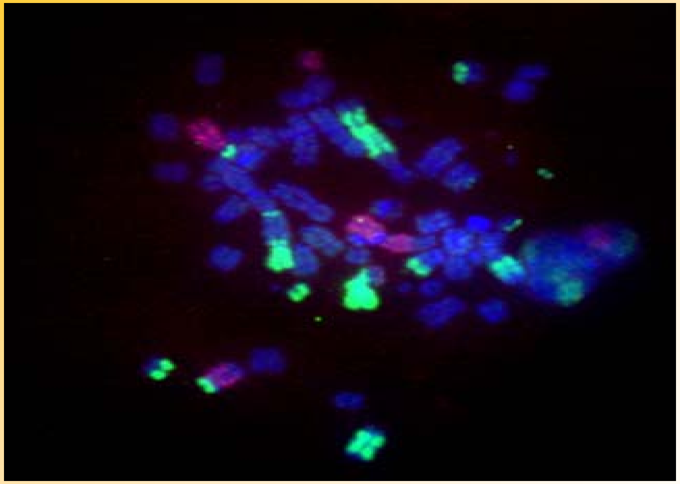
Counting statistics and distribution of fragment lengths from the LEM (Local Effect Model)

Distribution of number of DSBs



Distribution of fragments' lengths

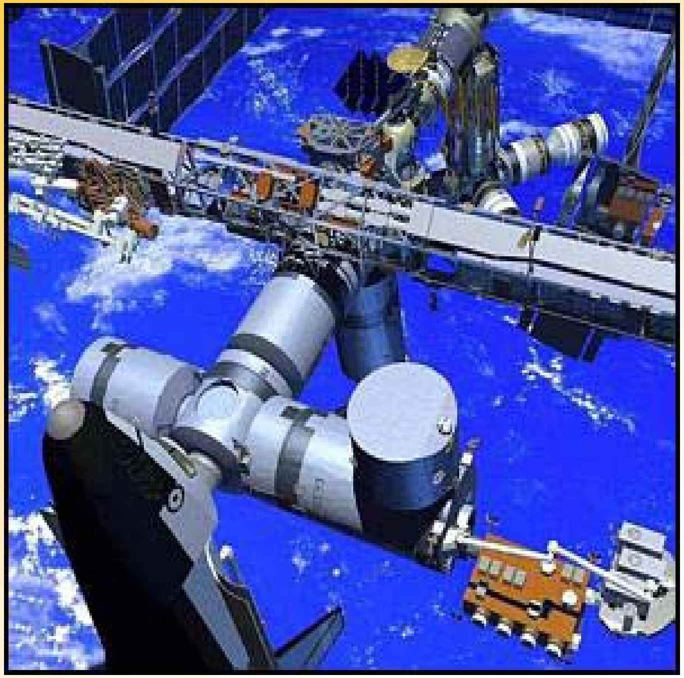




Conclusions

- After high LET irradiation most DSBs is located in clusters corresponding to multiply damaged sites
- Even without detailed information on chromatin geometry, stochastic models can give predictions on the frequency distribution of damage (DSBs, PCC plus excess fragments...)
- Differences in the complexity of induced lesions can be traced back to the pattern of a local energy (dose) deposition

Conclusions



Durante, 2003

- Cosmic radiation is one of the main problems for long-term space missions, particularly for the exploration of Mars

- Necessity: to reduce uncertainty in risk estimates and to develop contermeasures

- These tasks can be accomplished (within 10-20 years) by extensive biological experiments at accelerators using p and heavy ions at $0.1<E<10$ GeV/n

Recent publications

- S. Ritter, E. Nasonova, E. Gudowska-Nowak M. Scholz and G. Kraft *Aberrations in V79 Cells Analyzed in First and Second Post-irradiation Metaphases*, Int. J. Radiat. Biol. 76 (2000) 149.
- .E. Gudowska-Nowak, S. Ritter, G. Taucher-Scholz, G. Kraft, *Compound Poisson Processes and Clustered Damage of Radiation Induced DNA Double Strand Breaks*, Acta Phys. Pol. 31 (2000) 1109.
- .E. Nasonova, S. Ritter, E. Gudowska-Nowak, G. Kraft, *High-LET Induced Chromosomal Damage: Time Dependent Expression*, Physica Medica 17 (2001) 198.
- .E. Gudowska-Nowak, A. Kleczkowski, G. Kraft, E. Nasonova, S. Ritter, M. Scholz, *Mathematical Models of Radiation Induced Mitotic Delay*, Physica Medica, 17 (2001) 161.
- .E. Nasonova, E. Gudowska-Nowak, S. Ritter and G. Kraft*, Analysis of Ar Ion and X-ray Induced Chromatin Breakage and Repair in V79 Cells*, Int. J. Radiat. Biol. 77 (2001) 59.
- . S. Ritter, E. Nasonova, E. Gudowska-Nowak and G. Kraft *Is high LET damage on chromosomes different from low LET damage?* Proceedings of the 3rd Wolfberg Meeting on Molecular Biology, Ermatingen, Schweiz,1999
- .S. Ritter, E. Nasonova, E. Gudowska-Nowak and G. *Kraft Mutation Expression in Chromosomes After Particle Irradiation* GSI Annual Reports, Darmstadt, Germany 1999.
- .S. Ritter, S. Berger, T. Grősser, P. Hessel, G. Kraft, E. Nasonova, K. Ando, E. Gudowska-Nowak *Quantification of high LET induced chromosome damage*, GSI Annual Reports, Darmstadt, Germany 2000.
- .S. Ritter, E. Nasonova and E. Gudowska-Nowak *Effect of LET on the yield and quality of chromosomal damage in metaphase cells: a time-course study*}, Int. J. Radiat. Biol. 78 (2002) 191.
- .T. Grősser, P. Hessel, S. Ritter, E. Nasonova, E. Gudowska-Nowak, *Use of human lymphocytes for radiation risk assessment*, GSI Annual Reports, 2001.
- .R. Lee, T. Grősser, P. Hessel, E. Nasonova, E.Gudowska-Nowak, S. Ritter, *Analysis of the cell cycle progression of unirradiated and irradiated human lymphocytes*, GSI Annual Reports, 2000.
- .S. Brons, K. Psonka, M. Heiss, E. Gudowska-Nowak, G. Taucher-Scholz, *Direct visualisation of heavy ion-induced DNA fragmentation by use of the Atomic Force Microscopy*, Radiation Oncology, (2003) in press.

Enlight

Nupecc

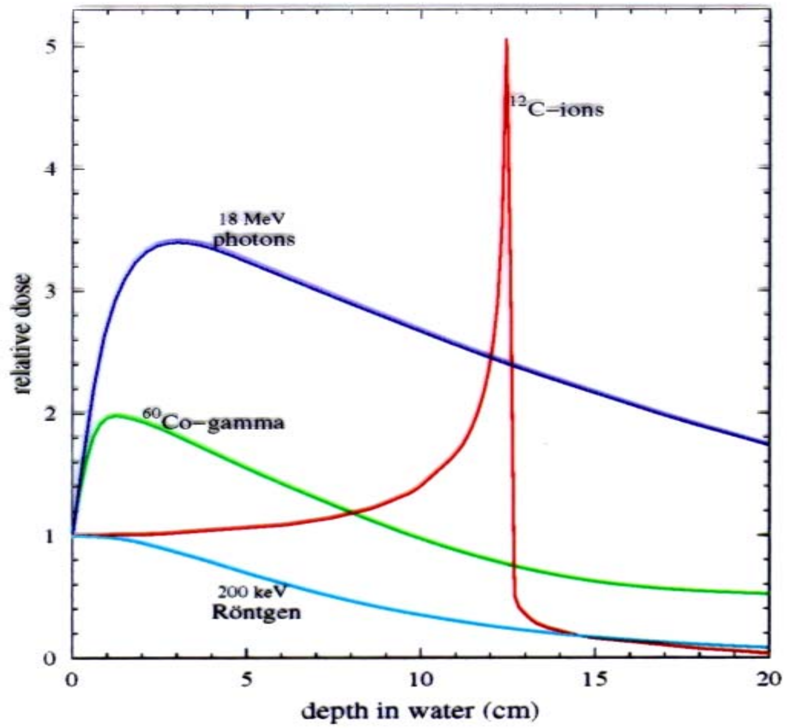
NANOsam

BiOLab

Nanometer-scale Science
Advanced Materials

NANOSAM UJ

Energy localisation: the Bragg peak



- Photons:

$$I(x) = I_0 e^{-\rho\sigma\frac{N_A}{A}\cdot x}$$

- Charged particles

$$S = -\frac{dE}{dx} \propto \frac{z^2}{\beta^2}\frac{Z}{A}\rho\left(\log\frac{2m_e\beta^2\gamma^2c^2}{I} - \beta^2\right)$$

Ni ions

3.5 MeV/u,

$4 \cdot 10^8$ p/cm^2

Induction of double strand breaks (DSB)