Trento Institute for
Fundamental Physics
and Applications

Recenti applicazioni del Local Effect Model a studi di radiobiologia

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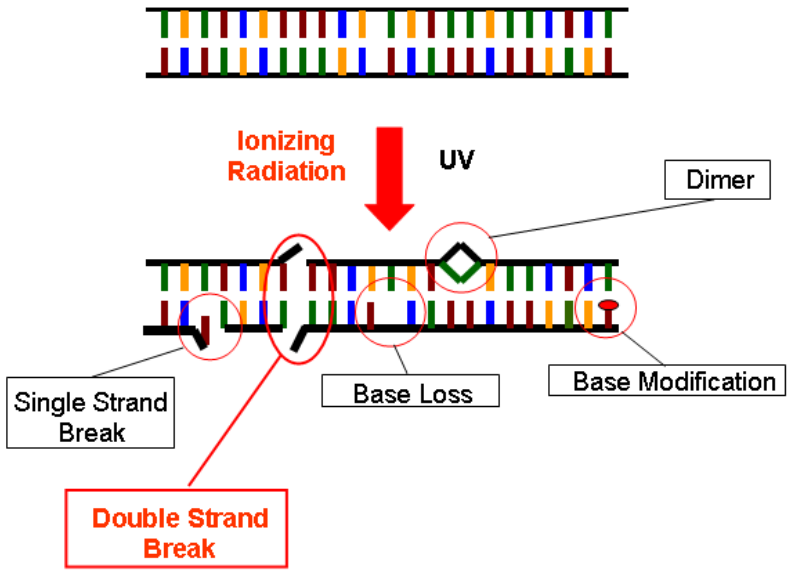
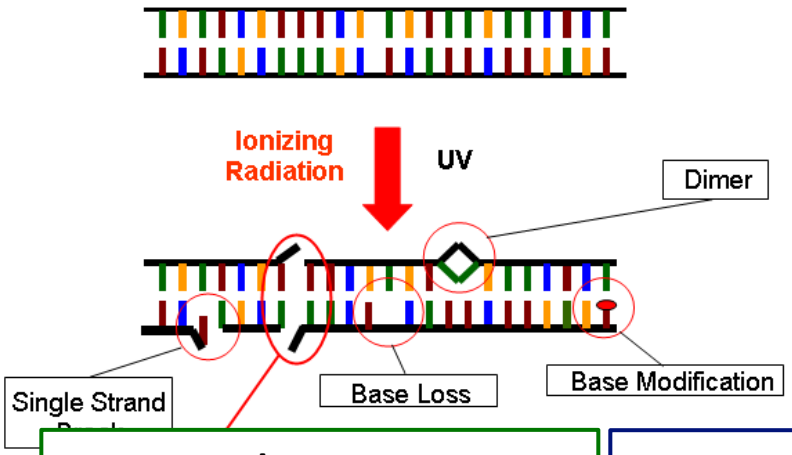
Congresso SIF 2015, Roma 21-25 Settembre

Basic concepts of radiation biophysics



- the DNA **Double Strand Break (DSB)** is considered the type of lesion most directly related to cell killing
- different radiation qualities produce the same spectrum of DNA lesions
- **BUT** the distribution of lesions inside the target can be very different

Basic concepts of radiation biophysics



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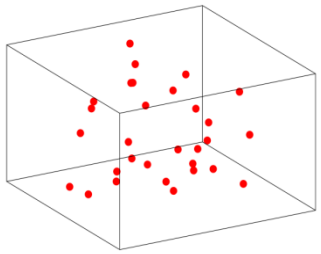
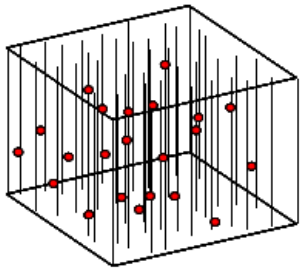
Photons
x-rays

Random
DSB distribution



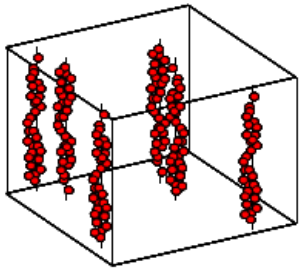
^{12}C Low LET
200 MeV/u, ≈ 16 keV/μm

Random
DSB distribution
(photon-like)



^{12}C High LET
1 MeV/u, ≈ 690 keV/μm

Non-random
DSB distribution
(RBE>>1)

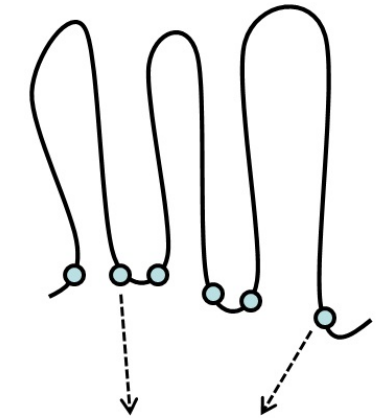


Modelling framework

- Framework: **Local Effect Model (LEM)**

- **Main ingredients:**
  - *Target (i.e. cell nucleus)*
  - *Amorphous track structure model*
  - *Photon dose response curve*

- Higher-order chromatin structure: **"Giant Loop Model"** of chromatin organization



DNA in cell nucleus:
≈ 6 x 10^3 Mbp

↓

Giant Loops: ≈ 2 Mbp

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Around 3000 domains of 2 Mbp (≈ 500 nm length)

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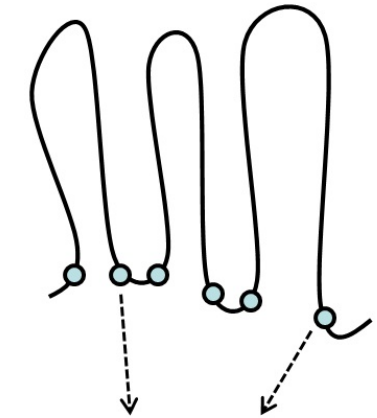

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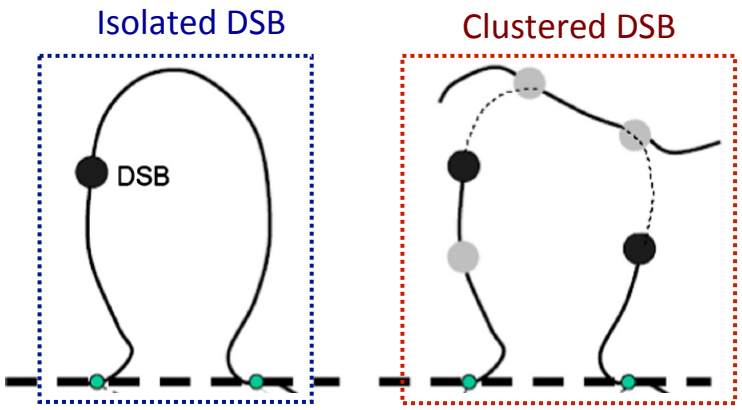

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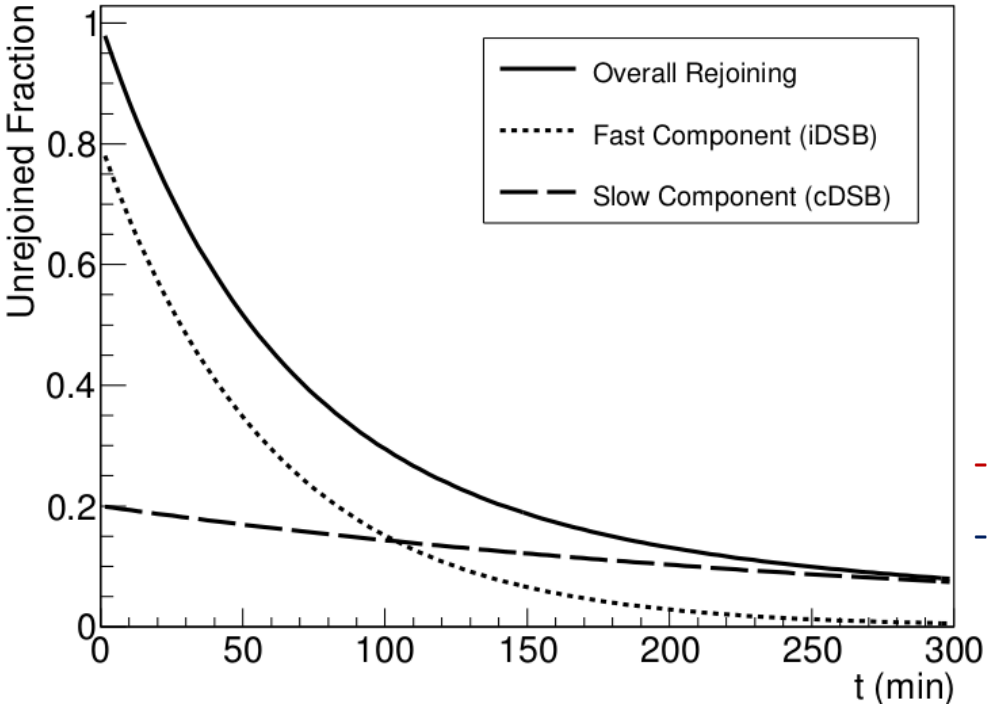
A DNA DSB kinetic rejoining model based on the LEM

DSB kinetic rejoining model based on the LEM



DSB rejoining: bi-exponential decay

iDSB ↔ fast component

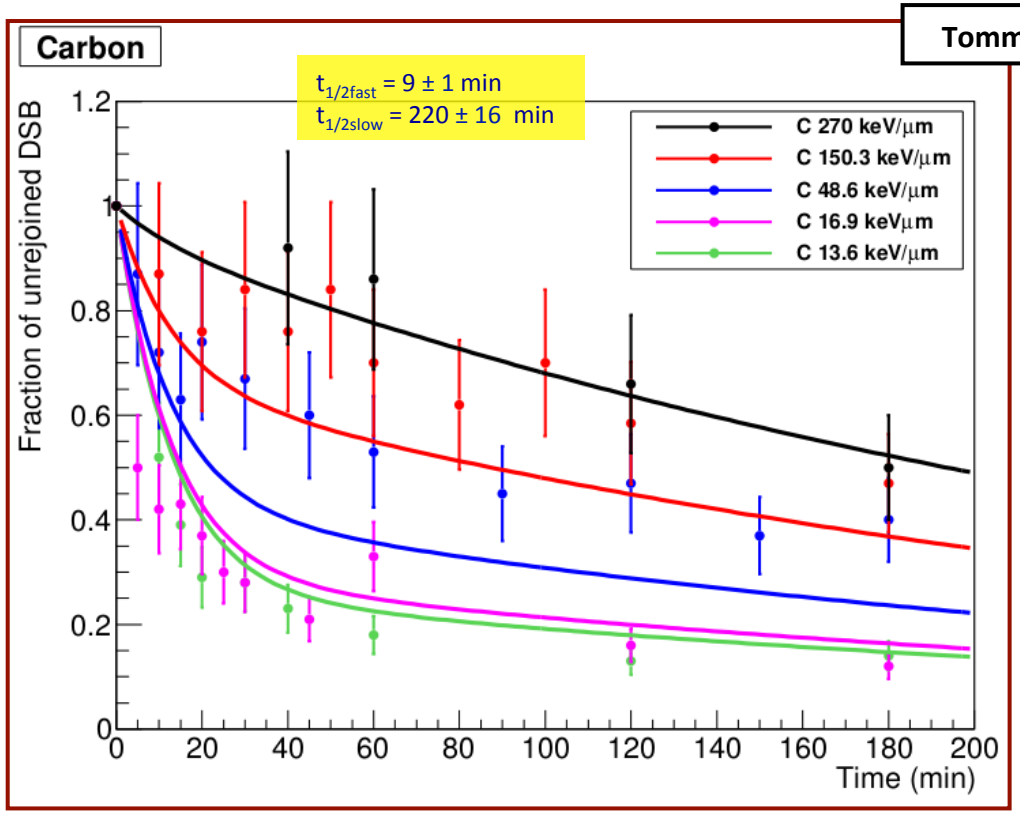
cDSB ↔ slow component

- **Input Values:** iDSB, cDSB (LEM calculated)
- **Fit Parameters:** half-lives fast and slow components

- **Differential effects entirely due to micrometer-scale clustering of DSB**
- **Simplistic approach:** e.g. chromatin condensation (EC/HC), different repair pathways not explicitly considered

DSB kinetic rejoining model based on the LEM

- Successful application to a **large data set** to describe DSB rejoining over time
- **Predictive power** of the model also tested



Tommasino et al 2013 Rad Res

Results support the **relevance of micrometer-scale clustering of DSB!**

CHO-K1 cells
gel electrophoresis

Track structure reconstruction based on γH2AX foci analysis

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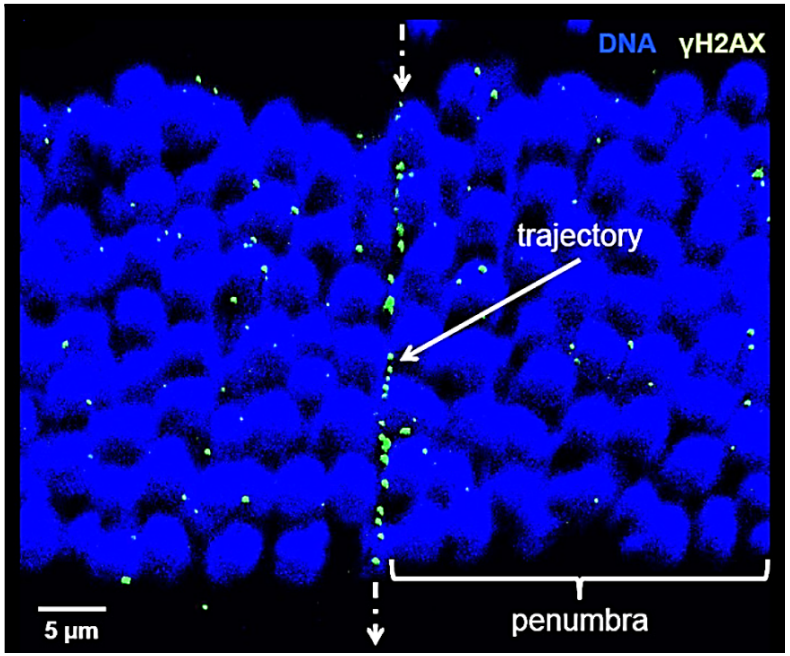
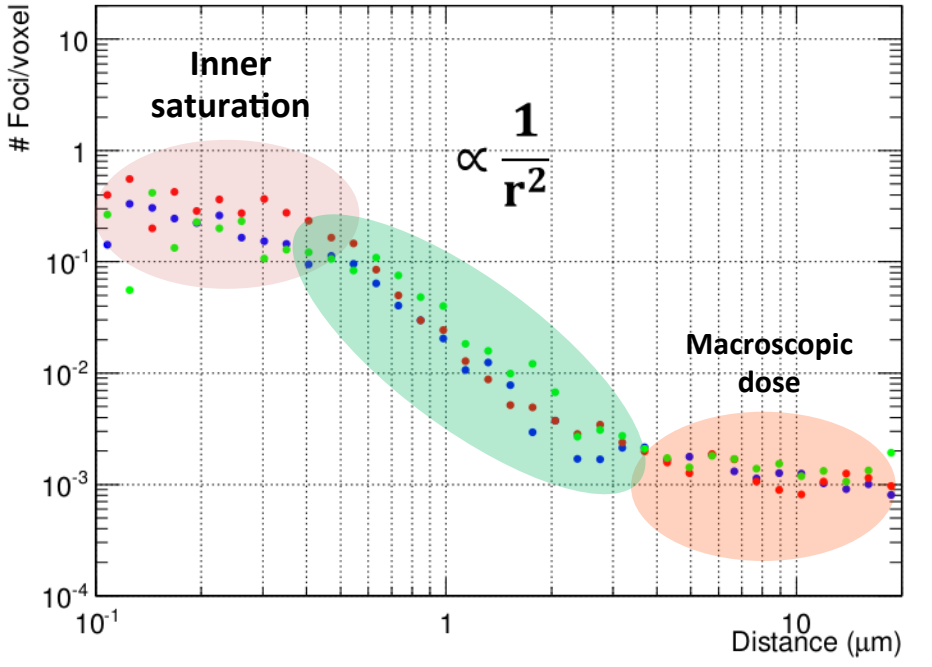


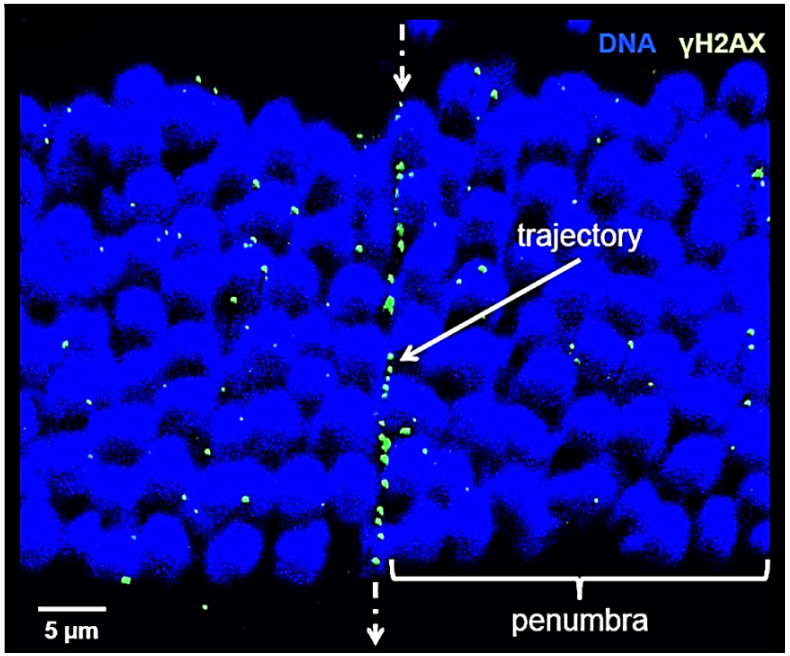
- **Mouse retina cells** (eyes irradiated ex-vivo)
- **Titanium ions** 114-129 keV/µm
- Fixation 15 min after irradiation
- DNA/γH2AX staining



- Microscopy analysis: **3D coordinates of cells and foci**
- Track reconstruction
- Modelling and statistical analysis

Mirsch et al 2015 PNAS

Track structure reconstruction based on γH2AX foci analysis



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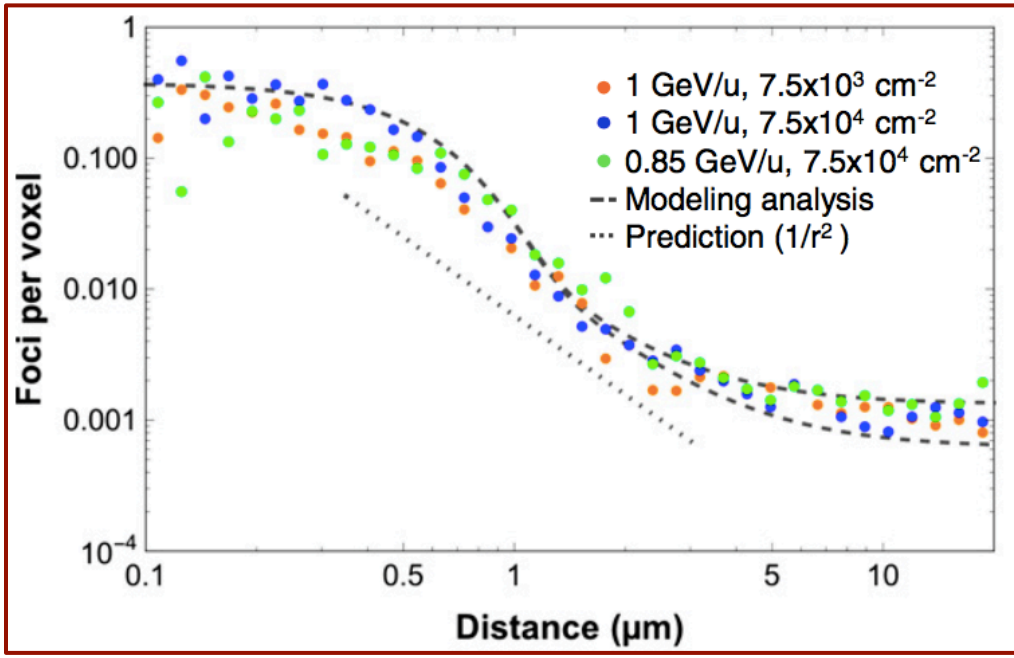

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Mirsch et al 2015 PNAS

Acknowledgements

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