Recenti applicazioni del Local Effect Model a studi di radiobiologia


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
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### Photons (x-rays)
- Random DSB distribution

### $^{12}$C, Low LET
- 200 MeV/u, $\approx 16$ keV/µm
- Random DSB distribution (photon-like)

### $^{12}$C, High LET
- 1 MeV/u, $\approx 690$ 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:**
\[ \approx 6 \times 10^3 \text{ Mbp} \]

**Giant Loops:** \[ \approx 2 \text{ Mbp} \]

**Around 3000 domains of 2 Mbp (\approx 500 \text{ nm length})**
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A DNA DSB kinetic rejoining model based on the LEM
DSB kinetic joining model based on the LEM

DSB rejoining: bi-exponential decay

- 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

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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

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

**Carbon**

\[
\begin{align*}
t_{1/2\text{fast}} &= 9 \pm 1 \text{ min} \\
t_{1/2\text{slow}} &= 220 \pm 16 \text{ min}
\end{align*}
\]

**CHO-K1 cells gel electrophoresis**

**Tommasino et al 2013 Rad Res**
Track structure reconstruction based on $\gamma$H2AX foci analysis
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- **Mouse retina cells** (eyes irradiated ex-vivo)
- **Titanium ions** 114-129 keV/$\mu$m
- Fixation 15 min after irradiation
- DNA/$\gamma$H2AX staining

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

*Mirsch et al 2015 PNAS*
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**Mirsch et al 2015 PNAS**
Acknowledgements