Mechanistic and phenomenological models of radiobiological damage

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Modelling radiobiological damage

General objective:
_to understand the mechanisms of radiation action on biological targets from physical interactions to biological damage, at sub-cellular, cellular, tissue, organ and systemic levels._

Specific objectives and methods:
development of sound based models (both mechanistic and phenomenological)
- to understand radiation action on biological systems
- to provide tools for predicting radiation risk (cancer and non cancer), particularly at very low doses!
- to optimize the clinical use of radiation (both in diagnostics and in therapy)
- to develop scientific bases for radiation standards
Diffusion

Dissociation: production of water radicals

Water

Irradiation

Primary interaction events

Biological molecules

Excitation and ionisation

Dissociation: production of water radicals

Diffusion

Damage to DNA and other molecules

DNA breaks

Chromosome aberrations

Damage at cell level

Damage at organ and organism levels

≈ 100,000 Ionizations
(≈ 2,000 in the DNA)

≈ 1,000 DNA ssb

≈ 40 DNA dsb

≈ 0.5-1 “complex lesions”

≈ 0.5-1 Chromosome Aberrations

≈ 0.5-1 Lethal lesions

≈ 10^{-5} HPRT mutations

≈ 10^{-5} neoplastic transformations

<< 10^{-8} cancers

1 Gy γ-rays in one nucleus

10^{-15} s

10^{-12} s

10^{-6} s

10^{-15} s

minutes

hours

years

Cross sections

Physics

Physics & chemistry

Chemistry

Biochemistry

Biology

Medicine

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≈ 2 nm
examples

Basic mechanisms
- Physical and chemical phases
- DNA damage
- Chromosome aberrations and cancer
- Bystander effect

Applications and phenomenological approaches
- Radiation protection in space
- Treatment planning
- Hadrontherapy
PARTRAC code
(Developed at GSF, Munich, with the collaboration of UniPv-DFNT, Pavia)

1. Irradiation conditions
   • Description of specific experimental arrangements or model scenarios by homogeneous bodies described via complex combinatorial geometry

2. Track structure calculations (Physical stage)
   • Electrons (Inelastic-scattering cross sections in liquid water [Dingfelder et al., 1998])
   • Photons (interaction cross section according to elemental composition of bodies)
   • Protons (Inelastic-collision cross sections in liquid water [Dingfelder et al., 2000])
   • Ions

3. Track structure time evolution (Physico-chemical and chemical stages)
   • Step by step approach for water radical transport (Ballarini et al, 2000)

4. DNA Target model (6 levels of organization) (Friedland et al, 1998, 1999)
   • Nucleotides (atomic description)
   • DNA double helix (including hydration shells)
   • Nucleosomes
   • Chromatin fiber (various arrangements tested)
   • Chromatin fiber loops
   • Loops connected to form chromosomes (organized in domains)

5. Damage induction models (e.g. ssb and dsb)
   • Ionisations inside van der Waals radii of DNA strand atoms (direct effect)
   • Ionisations inside water shell attached to phosphate and sugar (quasi-direct effect)
   • Interaction of OH-radical with deoxyribose (indirect effect)

6. Scoring of (Friedland et al, 1999):
   • Number and complexity of ssbs, dsbs, base damages
   • Spatial distribution of ssbs and dsbs and resulting size distribution of small DNA fragments (< 5 kbp from single tracks) and large DNA fragments (including inter-track effects and chromosomal breaks)
   • Patterns of partial and total deletions of HPRT exons induced in human fibroblasts

7. Biological end-points at cell level:
   • ..........................................................
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protons
\( \alpha \)-particles

\[
\begin{array}{c}
\text{LET [keV/\mu m]} \\
234 \\
165 \\
105 \\
79 \\
64 \\
\end{array}
\]
Carbon ions

LET [keV/μm]

740

415

MeV/amu

1

3

10nm
“Classical” Concepts of Track Structure Analysis

1. Nearest Neighbour Analysis:

2. Activation centered Neighbourhood Analysis:

3. Track Entities:

4. Cluster Formation:

5. Cluster Association:
PARTRAC CODE
EXAMPLE OF TRACK STRUCTURE (300eV electron):
OUTPUT OF THE PHYSICAL MODULE ETRAC
(INPUT OF THE PHYSICO-CHEMICAL AND CHEMICAL MODULES)

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Int. = interaction type:
2: elastic scattering
3-7: excitations
8-12: ionisations

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Track structure and time evolution: parameters

Physical stage $\rightarrow \approx 10^{-15}$ s:
- cross sections

Prechemical stage ($\approx 10^{-15} \rightarrow 10^{-12}$ s)
- Dissociation schemes
- Product positioning
- Thermalisation distance

Chemical stage ($\approx 10^{-12} \rightarrow 10^{-6}$ s)
- Diffusion coefficients
- Reaction rate constants
  - Radical-radical
  - Radical-scavenger
  - Radical-DNA

Elastic, ionisation, and excitation cross sections for electron impact on water vapor (Paretzke 1989)
$\text{H}_2\text{O}$

$10^{-15}\text{s} \quad \text{H}_2\text{O}^*$

$\rightarrow$ autoionisation

$\rightarrow$ $\text{H}_2\text{O}^+ + e^-$

Relaxation

Dissociation

Thermalisation

$10^{-12}\text{s} \quad \cdot\text{OH} \quad \cdot\text{H} \quad \cdot\text{O} \quad \text{H}_2 \quad \text{H}_2\text{O}_2 \quad \text{H}_3\text{O}^+ \quad e^-_{\text{aq}}$

diffusion and reaction

$10^{-6}\text{s} \quad \text{chemical equilibrium}$
Time evolution of the track in pure water

- Model predictions (Ballañini et al)
- Experimental data (from Fulford et al, 1999)

**Graphs:**
- Graph showing the time evolution of electron track energy in pure water for different times.
- Graph showing the OH yield (μmol J⁻¹) for different electron track energies at time t = 10⁻⁶ s.
- Graph showing the mean free path for electron inelastic scattering for different energies.
From the geometrical model to an atomic description of DNA

Charlton et al (IJRB 1989)
Differences alpha particles – protons

Relative Biological Effectiveness for Inactivation and Mutations (experimental) ⇒ vs DNA Complex Lesions (simulated)

(Belli et al. 1989......1998 ....)

Complex Lesions (PARTRAC simulations)
Figure 2. Calculated yields of ssb (panel a) and dsb (panel b) for different DNA structures (linear DNA, SV40 minichromosome and cellular DNA) as a function of the Scavenging Capacity (scale at the bottom) and the DMSO concentration (scale at the top).
Uncoupling the effects of target structure and scavenging capacity

DSB yields vs dose
- cellular DNA
- linear DNA at cellular scavenging capacity
- linear DNA at a reduced scavenging capacity of $8.85 \times 10^6$ reactions/s
(Data are from Nygren et al. 1995)

Ballerini et al., Radiotherapy and Oncology, Dec. 2004
DNA Double Strand Breaks induced in human cells by charged particles and γ-rays: Experimental Procedure

Cells: AG1522 human fibroblasts

1. Cells cultured in the presence of $^{14}$C-thymidine or $^3$H-thymidine

2. IRRADIATION (γ-rays, protons)

3. Cells detached, centrifuged and resuspended in low gelling agarose

4. Formation of gel plugs (75 μl with 1x10⁶ cells each)

5. Plugs incubated at 50°C in the presence of Proteinase K and Sarkosyl

6. DSB detected by gel electrophoresis (PFGE) using the fragment counting method

PFGE (conditions A)
size range: 1000-5700 kbp

PFGE (conditions B)
size range: 23-1000 kbp

Belli et al, ISS, Rome
Calculated and measured fragment size distribution following irradiation with 100 Gy of 0.84 MeV protons.
Learning from discrepancies and conflicting evidences

Dose-responses for γ-ray-induced DSB in human fibroblasts

![Graph showing dose-response for γ-ray-induced DSB in human fibroblasts. The graph plots DSB (Mbp⁻¹) against D (Gy) with different markers representing different size ranges of DSBs.](image)
Modelization of DNA fragmentation induced in human fibroblast by 115-MeV/u Fe-56 ions

(In preparation, collaboration UniPv and ISS (Italy), GSF (Germany))
Modelization of DNA fragmentation induced in human fibroblast by Fe-56 ions (cont.)

Preliminary results:

- Where measures are available (1-5700 kbp), PARTRAC predictions are in good agreement with experimental data.

- Fragments < 1 kbp (in the non measured range) predicted by PARTRAC are ≈ half of the total number of ion induced DNA fragments

⇒⇒⇒ experimental RBE for dsb (1-5700 kbp): 1.34

calculated RBE for dsb (all sizes) : 2.39

(In preparation, collaboration UniPv and ISS (Italy), GSF (Germany))
A Monte Carlo code for the induction of chromosome aberrations

The target

Basic assumptions
- Chromosome aberrations arise from clustered DNA breaks
- A chromosome exchange requires (at least) 2 radiation-induced lesions
- Only free ends in neighboring chromosome territories or in the same territory can give rise to an exchange

The simulation scheme

- Identification of hit chromosomes
  - Free-end interaction
  - Scoring (Giemsa or FISH)
  - Repetition for at least 100,000 cells

- Dose
  - CL Gy^-1 Da^-1
  - CL traversals/cell
  - CL traversals (along the tracks)

- Gamma rays
- Light ions

- Background
Radiation induced chromosome aberrations

Comparison experiments - simulations

1 chromosome painted

3 chromosomes painted


Data: Finnon et al. 1999, IJRB


Data: Ballarini and Ottolenghi, Rad Environ Biophys, 3 (2004)
a (preliminary!!!) approach for modelling CA induction by heavy ions:

2nd step: to use DNA lesion spatial distributions obtained by the PARTRAC code (in coll. with GSF)
A pilot study on Chronic Myeloid Leukemia risk estimation

Starting argument: CML is caused by a BCR-ABL translocation between chromosomes 9 and 22 of primitive hematopoietic stem cells

“Overall look” up to ≈1 Gy: linear  “Zoom” below ≈ 0.1 Gy: quadratic

Ballarini and Ottolenghi, REB, 2004
“New” Challenging topics (e.g. “nontargeted” and delayed effects)

Radiation induced bystander effect:

*Damage induction in cells not directly hit by radiation*

- A
- B
- C
- D
- E

Genomic instability

Heritable, genome-wide process of instability that leads to a persisting enhanced frequency of genetic and functional changes in the non-irradiated progeny

*from W.F. Morgan, Rad. Res. 159 (2003)*

*Goldberg and Lehnert, IJO, 2002*
### Bystander effect: Possible signals

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<th>via Extracellular Environment</th>
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<td>• Ca**+**</td>
<td>• Cytokines, e.g.:</td>
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<td>• c-AMP (cyclic-AMP)</td>
<td>- IL-2 (Interleukin-2)</td>
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<td>• Antioxidants (thiols)</td>
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<td>• (long-lived) organic radicals</td>
<td>- TNFα (Tumor Necrosis Factor- α)</td>
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<td>• Nitric Oxide</td>
<td>• TGFβ (Tumor Growth Factor- β)</td>
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<td>• Lipid peroxidation products</td>
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ROS (Reactive oxygen species: H₂O₂, O₂⁻, etc.)
Bystander effects: some mechanisms

Coates et al. 2004, Mutat Res 568, 5
Methods
(Based on Monte Carlo simulations)

- 840 cells over a $10 \times 10 \text{ mm}^2$ grid (0.35 mm step)
- Signals starting from the cell surface
- Pure diffusion
- Reaction if distance $\leq 10 \mu m$ (Nikjoo et al. IJRB)

- Step-by-step random walk simulation
  - $\lambda = \sqrt{r^2} = \sqrt{6D\Delta t}$
  - $D = 10^8 \text{ nm}^2/s$
examples of simulation outcomes

signals starting from the irradiated cell

signals starting also from unirradiated cells

signals randomly distributed in the medium

Prise et al. 1998 IJRB
Time dependence of signal (citokine) concentration in the medium

CULTURE MEDIUM

Feedback and signal depletion

Signal degradation
cytokine ➔ scavenger
(e.g. enzyme)

Signal release

? Enzymes
cells

Perturbing agents
(radiation)
Some considerations on bystander effects

- Different signals are generally involved simultaneously in cell communications.
- Different experimental conditions may select the different signals, modifying the response of bystander cells.
- Different concentrations of the same signal may produce different (even opposite) effects.

As a consequence:

- *In vivo* cell and tissue bystander response, may dramatically differ (both qualitatively and quantitatively) from *in vitro* cell response.
Examples of “phenomenological” and “pragmatic” approaches
INTEGRATION OF RADIOBIOLOGICAL DATA AND CALCULATIONS INTO RADIATION TRANSPORT CODES

Radiobiological data and results of simulations (distributions) based on track structure codes (e.g. PARTRAC) and biophysical models (e.g. radiation induced CA models and codes)

Radiation field and irradiation geometry → Condensed history M.C. code (e.g. FLUKA) including models to evaluate mixed-field effects → Doses, Fluences...; effects at cellular, organ and organism levels
Mixed fields

Galactic Cosmic Rays

**spectrum:** 87% protons, 12% He ions and 1% heavier ions (fluence) with peaks at 1 GeV/n

**flux:** $\sim 4$ particles/(cm$^2$ s) at solar min.

**dose:** $\sim 1$ mSv/day

Solar Particle Events

**spectrum:** 90% protons, 10% heavier ions with energy mainly below $\sim 200$ MeV

**flux:** up to $\sim 10^{10}$ particles/cm$^2$ in some hrs.

**dose:** order of Sv, strongly dependent on shielding and organ

*NASA pub. 1998*
The main contribution is given by primary protons, even if secondary hadrons become more important for internal organs (for the liver such contribution increases from 14% to 60%, for the skin from 7% to 46%, as the Al thickness increases)
FROM DNA DAMAGE TO CELL INACTIVATION
Mixed fields conditions: a fully modulated therapeutic proton beam

Complex Lesions as a function of LET and particle type

FLUKA CODE (EXTENDED)

Theor. predictions
Experim. data

72 MeV proton BEAM

Biaggi et al NIM-B, 1999, 159,89-100
Characterization of a “virtual” 160 MeV proton beam

absorbed dose

“biological” dose

Target characteristics

Example: Normal Tissue Complication Probability (NTCP)

- FSUs = Tissues may be considered to be composed of functional subunits (FSUs) which are responsible for the total organ/tissue function.
  - e.g. Nephron (kidney), Alveolus (lung), 0.1 cm² of cutis
- Critical element (serial) tissue = the effect appears if at least one FSU is inactivated
- Parallel element tissue = the effect appears if a certain portion of FSUs is inactivated

\[ \prod = \text{where:} \]

\[ P_c = \left[ 1 - \prod_{i=1}^{n} \left[ 1 - P(D_i)^s \right]^{ΔV} \right]^{1/s} \]

Where:

- The relative seriality \( s \) is the ratio between the number of serial subunits and the total number of subunits.
- \( P(D) \) is the dose response curve of the organ
- \( v \) is defined as \( v / V \), where \( v \) represents each subvolume in the DVH and \( V \) is the volume of the whole organ.
Mixed fields: Hadrontherapy with Carbon ions
270 MeV/u Carbon beam
Beam composition after 10 cm of water

Mixed Field

+ energy spectrum of each ion type!
Mixed fields: Hadrontherapy with Carbon ions

SURVIVAL PARAMETER DATA BASE (e.g. $\alpha$, $\beta$, etc.) calculated as a function of particle types and energies (e.g. using LEM or NIRS approaches)

spatial distribution of fluences → model (and code) to calculate “weighted averages” of parameters in mixed fields → Spatial distribution of biological dose
The Local Effect Model (LEM) (Scholz, ...1994.....)
(based on an amorphous description of the ion track (no track structure))

**Principles of the Local Effect Model:**
- The radial dose distribution of the track is divided into zones of nearly equal dose.
- The probability to produce a lethal lesion in each zone is calculated according to the X-ray dose effect curve.

\[ N_{\text{lethal}} = \text{average number of lethal events} \]

\[ N_{\text{lethal}} = \int \int \int \frac{-D(x,y,z)}{V} \, dx \, dy \, dz \]

\[ S_{\text{Ion}} = e^{-N_{\text{lethal}}} \]
A Microdosimetric approach

\[ Y(D) = \int \varepsilon(z) f(z, D) dz \]

Where:

- \( Y(D) \) = effect as a function of the macroscopic dose \( D \)
- \( z \) = specific energy
- \( \varepsilon(z) \) = response function
- \( f(z, D) \) = specific-energy frequency characterising an irradiation with a macroscopic dose \( D \)

- The response function \( \varepsilon(z) \) is calculated through an unfolding procedure starting from experimental data, given \( f(z, D) \) and \( Y(D) \)
A Microdosimetric approach in radiotherapy

\[ RBE = \int P(y)d(y)dy \]

The weighting function \( P(y) \) has to be unfolded starting from the microdosimetric spectrum and radiobiological experimental data on RBE.

The main limits of the approach are probably:

- the reference volumes considered,
- the “role” given to the lineal energy \( y \),
- the “risks” intrinsically present in unfolding procedures (to calculate \( P(y) \)), and
- the experimental difficulties in measuring \( d(y) \), in the region of \( y \) values corresponding to the maximum in \( P(y) \).
Thank you for your attention!!

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