TO THE MECHANISM OF CELL INACTIVATION BY LIGHT IONS AT DIFFERENT ENERGY VALUES

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1. Introduction

Realistic mathematical models of radiobiological effect
- Better understanding of corresponding mechanism
- Influence of individual processes
  - Radiomodifiers, oxygen effect, dependence on linear energy transfer, etc.
- Optimization in clinical radiotherapy

2. Probabilistic two-stage model

- 2 different phases of radiobiological mechanism
  - Energy transfer events and formation of individual DNA damages
  - Biological reaction of a cell to cumulative damage

- **Basic scheme** (simplified for monoenergetic particles) [1-4]
  - **Number k of particles** traversing chromosomal system (energy transfer events)
    - Average number $n=hD=C\sigma D/\lambda$
      D...applied dose
      h...number of particles per unit dose
      σ…effective cross-section of cell nucleus (chromosomal system)
      C…conversion constant, C=6.24 keV Gy^{-1} μm^{-3}
      λ…linear energy transfer (LET)
    - Poisson distribution:
      $P_k = \exp(-hD) \cdot (hD)^k / k!$
  - Subsequent **inactivation probabilities:** $p_k \leq p_{k+1}$
  - Probability of **cell survival**:
    $s(D)=1-\sum_k P_k p_k$

- **Low-dose region:** polynomial expansion
  $s(D)=\exp[-\sum_k \alpha_k D^k]$, α_k – functions of p_k (and vice versa)
  - Significant deviations from parabolic shape (linear-quadratic model) [1]; experimental evidence [5]

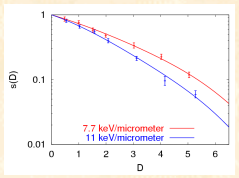
- **Inactivation probabilities p_k – detailed mechanism**

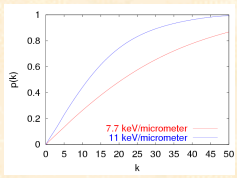
  A. Formation of **irreparable damage** by an individual particle
  … probability **$a(\lambda)$**
  - Probability of no damage after k hits: $q_k^A = (1-a(\lambda))^k$

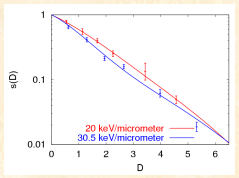
  B. Formation of **severe but reparable damage** by an individual particle
  … probability **$b(\lambda)$**
  (e.g., severe damage of only 1 chromosome in given homologous pair)
  - Combination of 2 or more such damages may inactivate the cell, if not repaired correctly
    (e.g., damages in corresponding segments of both homologous chromosomes)
    …probability of not being damaged: $(1-b^2(\lambda))^{k(k-1)/2}$
  - Probability of **successful repair** … **$r(k,\lambda)$**
    - Decreasing with k and λ – damage complexity increases
  - Survival probability
    $q_k^B = 1 - [1 - (1-b^2(\lambda))^{k(k-1)/2}] \cdot [1 - r(k,\lambda)]$
  - Cell survival probability – both phenomena:
    $q_k = q_k^A \cdot q_k^B$
- **Inactivation probability $p_k = 1 - q_k$**

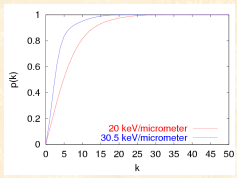
3. Analysis of experimental data

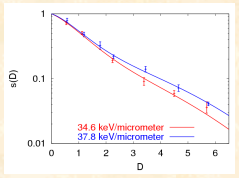
- Irradiation of V79 cells by low-energy protons – data taken from Belli et al. [6]

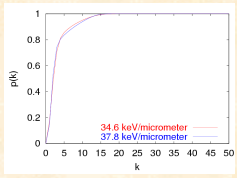












• Survival curves • Inactivation probabilities

- Model functions used for $a(\lambda)$, $b(\lambda)$, $r(k,\lambda)$:
  - Flexible test functions with low number of free parameters

$$a(\lambda) = (a_1\lambda + a_2\lambda^2)[1-\exp(-(a_3\lambda)^{a_4})]$$

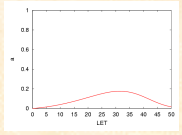
$$b(\lambda) = \frac{[1-\exp(-(b_1\lambda)^{b_2})]}{[1+b_3\exp(-(b_4\lambda)^{b_5})]}$$

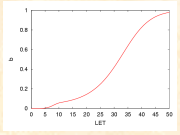
$$r(k,\lambda) = 1 - \frac{[1-\exp(-(r_1 k\lambda)^{r_2})]}{[1+r_3\exp(-(r_4 k\lambda)^{r_5})]}$$

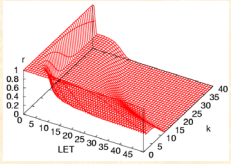
  - Auxiliary parameters $a_1 \ldots a_4$, $b_1 \ldots b_5$, $r_1 \ldots r_5$
  - Parameter values (effective cross-section of cell nucleus σ=12.8μm^2; average geometrical cross-section of cell nucleus σ_n=134 μm^2 [6]):

a_1=0.0022	a_2=0.013	a_3=0.026	a_4=5.0	
b_1=0.12	b_2=5.0	b_3=24.1	b_4=0.061	b_5=1.76
r_1=0.024	r_2=5.0	r_3=0.56	r_4=0.0021	r_5=5.0

  - Total χ^2 value: 24.0, $\chi^2|_{DF}$=0.97 (LQ model: χ^2=45.0, $\chi^2|_{DF}$=1.67)







• Probability of irreparable damage formation, $a(\lambda)$
• Severe but reparable damage formation probability, $b(\lambda)$
• Probability of successful repair, $r(k,\lambda)$

- Results:
  - Saturation of irreparable damage formation
  - Increasing probability of formation of reparable damage
  - Probability of successful repair decreasing with linear energy transfer and/or number of traversing particles – increasing damage complexity

4. Conclusion

- General two-stage model of cell inactivation
  - Systematic description of experimental data
  - Detailed structure of cell survival curves (important for fractionation)
  - Realistic model scheme
    - Irreparable damage by individual particles ("direct inactivation")
    - Reparable damage
    - Characteristics of repair processes
- Basis for microscopic modelling of radiobiological effect
- More precise and systematic experimental data needed to establish detailed characteristics of underlying mechanisms

- Future aims:
  - Systematic analyses of ion data, comparison with track-structure models
  - More detailed models for inactivation probabilities – mechanistic basis (ionization, radical clusters, DNA damage formation, repair processes)

5. References

[1] Judas L., Lokajíček M.: Cell Inactivation by ionising particles and the shapes of survival curves. *Journal of Theoretical Biology* 210 (2001), 15-21

[2] Lokajíček M., Judas L., Kundrát P.: Bragg peak, model of radiobiological mechanism and relative biological efficiency of different ions. 8th HCPBM, Baden bei Wien, 2002 (to be published in the proceedings)

[3] Kundrát P.: Probabilistic model of cell inactivation by ionising particles. Week of Doctoral Students 2003, Faculty of Mathematics and Physics, Charles University in Prague (to be published in the proceedings)

[4] Kundrát P., Lokajíček M., Hromčíková H.: Cell inactivation by diverse ions along their tracks. Submitted to *Journal of Theoretical Biology*

[5] Schettino G., Folkard M., Prise K.M., et al.: Low-dose hypersensitivity in Chinese hamster V79 cells targeted with counted protons using a charged-particle microbeam. *Radiation Research* 156 (2001), 526-534

[6] Belli M., Cera F., Cherubini R., et al.: RBE-LET relationships for cell inactivation and mutation induced by low energy protons in V79 cells: further results at the LNL facility. *International Journal of Radiation Biology* 74 (1998), 501-509