ION TRACKS AND CELLULAR REPAIR MECHANISMS OBSERVED IN RADIATION DOSE RESPONSE CURVES

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The dose-response curves are usually described by a linear-quadratic (LQ) model using the tissue specific α and β parameters, Y = α D + β D^2. Since the ab initio Monte Carlo simulations starting with formation of the ion track structures cannot correctly describe the final biological effects, phenomenological models are still necessary. Especially, the strengths of repair mechanism of double strand breaks of DNA at low doses is of large interest in radiobiological research. In the present work, we study the LQ model of response curves obtained for different ionizing radiations and apply the approach of the effective ion track radius to distinguish between the physical and biological effects contributing to the curvature of the dose response relation. Since the effective interaction radii determined from the experimental dose-effect curves are much larger than the physical values, we conclude that the biological component resulting from the cellular repair processes dominates.

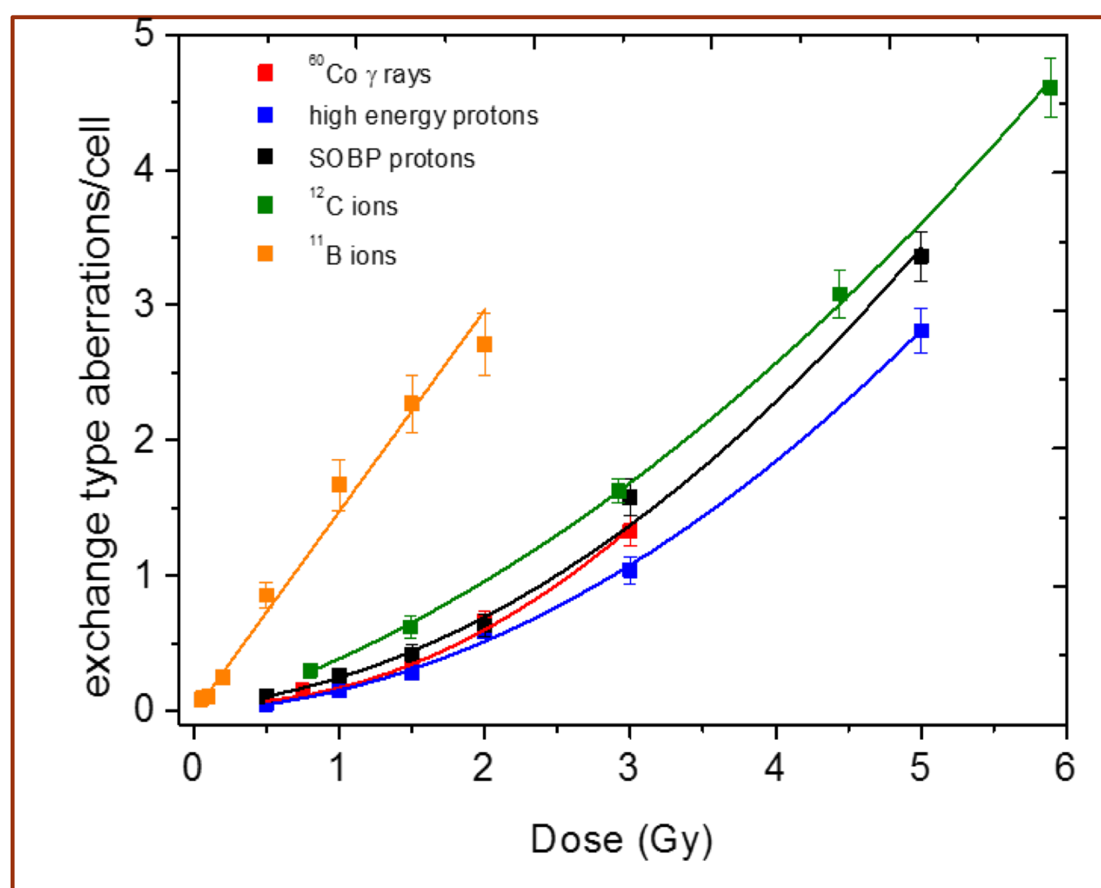

Fig. 1 Dose dependence of exchange type aberrations per single cell

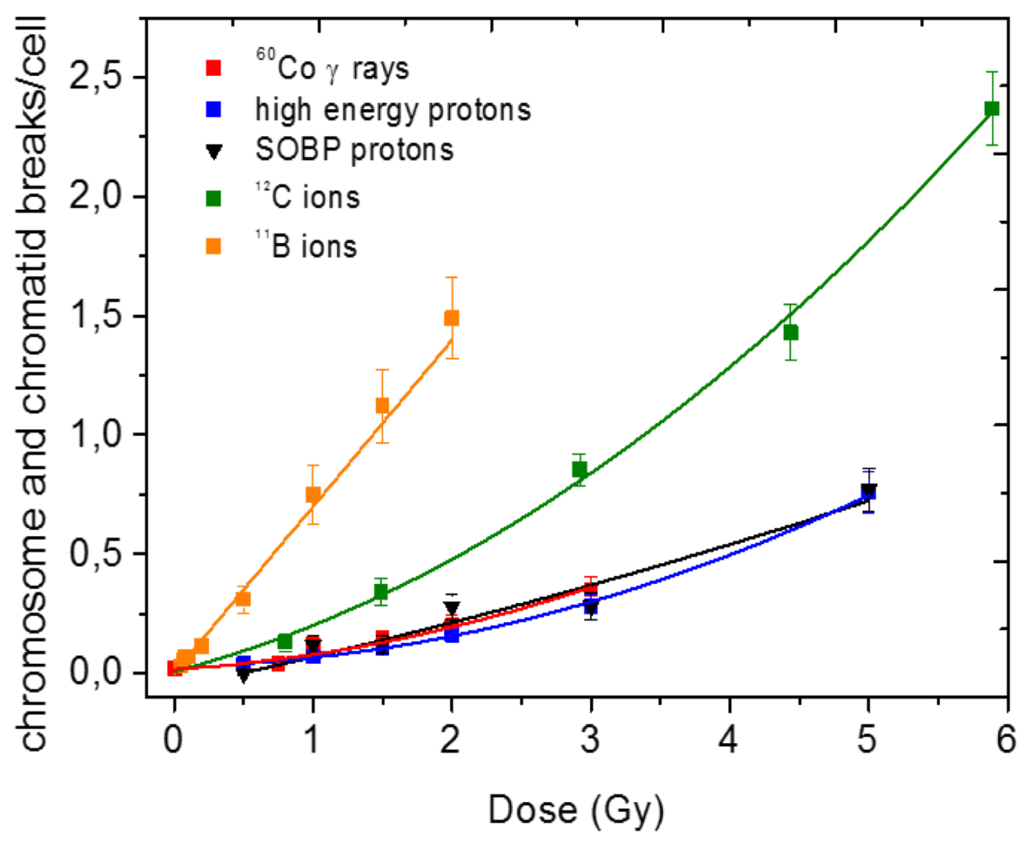

Fig. 2 Dose dependence of chromosome and chromatid breaks per single cell

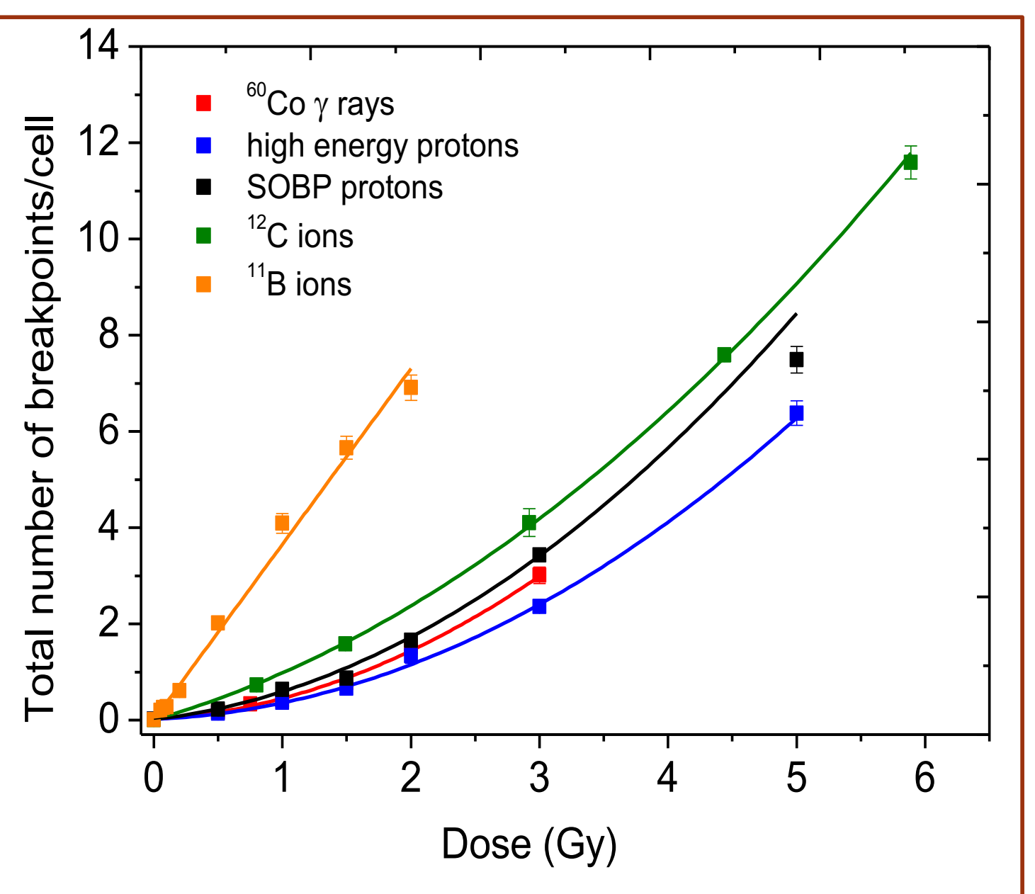

Fig. 3 Dose-effect curves plotted for all scored chromosome aberrations per single cell

Table 1

Dose-effect curve	fit parameters	^{60}Co γ rays	high energy protons	SOBP protons	^{12}C ions	^{11}B ions
Chromosome and chromatid breaks /cell	α	0.036±0.033	0.01±0.03	0.12±0.04	0.15±0.03	0.69±0.05
	β	0.026±0.013	0.027±0.008	0.0067±0.0091	0.04±0.01	-
	int.	0.017±0.013	0.029±0.025	- 0.06±0.02	0.009±0.010	0.004±0.008
Exchanges / cell	α	- 0.05±0.12	0.058±0.051	0.10±0.08	0.34±0.11	1.48±0.08
	β	0.16±0.04	0.10±0.01	0.12±0.02	0.08±0.02	-
	int.	0.06±0.07	- 0.006±0.003	0.03±0.06	-0.03±0.11	- 0.01±0.02
Total aberration yield / cell	α	0.096±0.051	0.07±0.03	0.18±0.04	0.46±0.06	2.17±0.09
	β	0.15±0.02	0.13±0.01	0.13±0.01	0.12±0.01	-
	int.	0.021±0.014	0.02±0.01	0.018±0.013	0.01±0.01	0.006±0.009

1.We introduce the effective physical radius R' which corresponds to the ion track radius of a constant dose density within the ion track:

$$R' = R_{min}\sqrt{1+2ln\frac{R_{max}}{R_{min}}}$$

Where R$_{min}$ and R$_{max}$ are track core and penumbra radii, respectively, calculated according to formulas given by:

$$R_{min} = \frac{v}{c}\cdot 0.0116\ (\mu m)$$

$$R_{max} = 0.768E - 1.925\sqrt{E} + 1.257\mu m$$

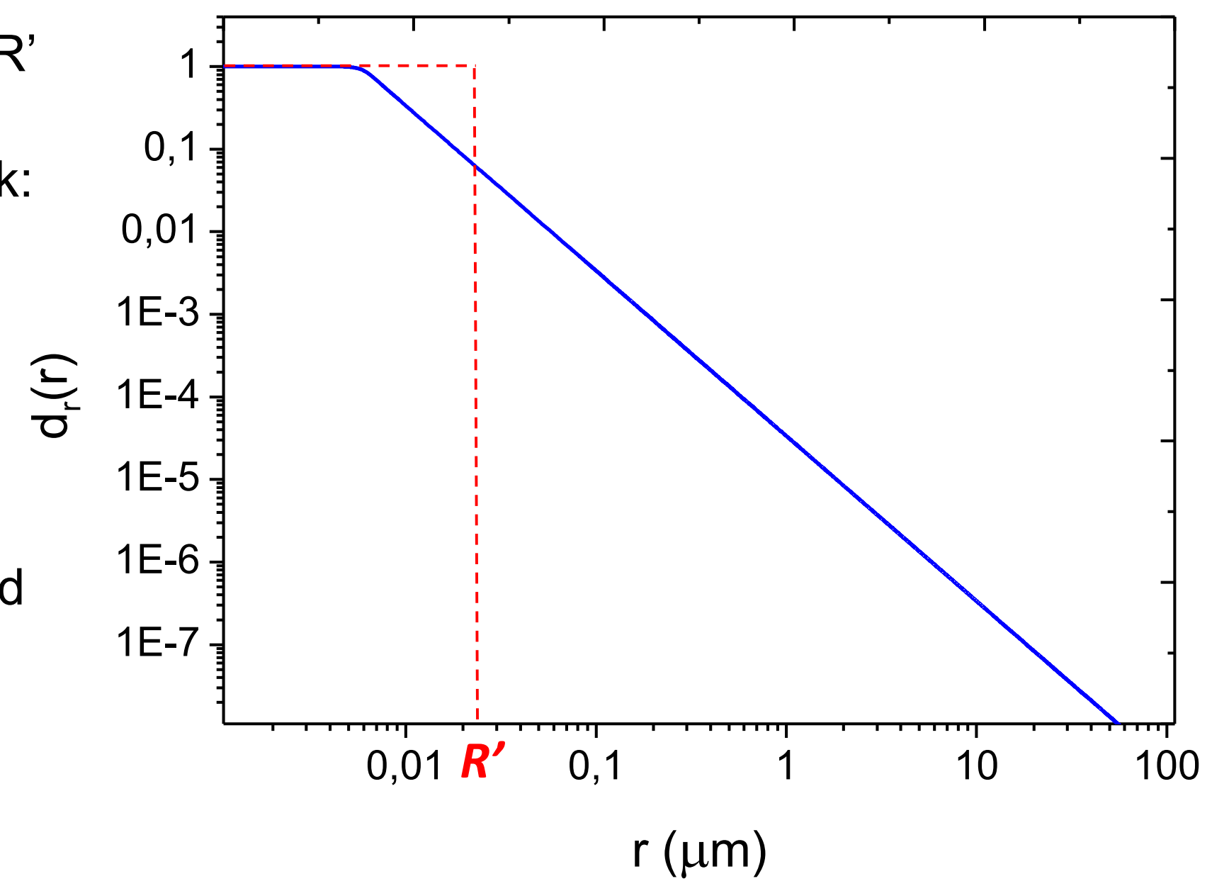

Fig. 4 Schematic illustration of the radial dose plotted for 150 MeV protons. Physical interaction radius R' represents the idea of a constant dose density within a given range

2. To investigate how large the ion track radius should be to explain the observed linear-quadratic response function we introduce effective interaction radius R based on the experimental results of dose response curves. The model is based on the assumption of absorption of a double dose in the overlapping track areas.

$$R = \sqrt{\frac{3\cdot LET}{8\cdot F\cdot \rho_m}}\cdot\sqrt{\frac{\beta}{\alpha}}$$

Where ρ_m is the material density, α and β parameters of the fitted dose-response relation (see Table 1) and F is a geometrical factor

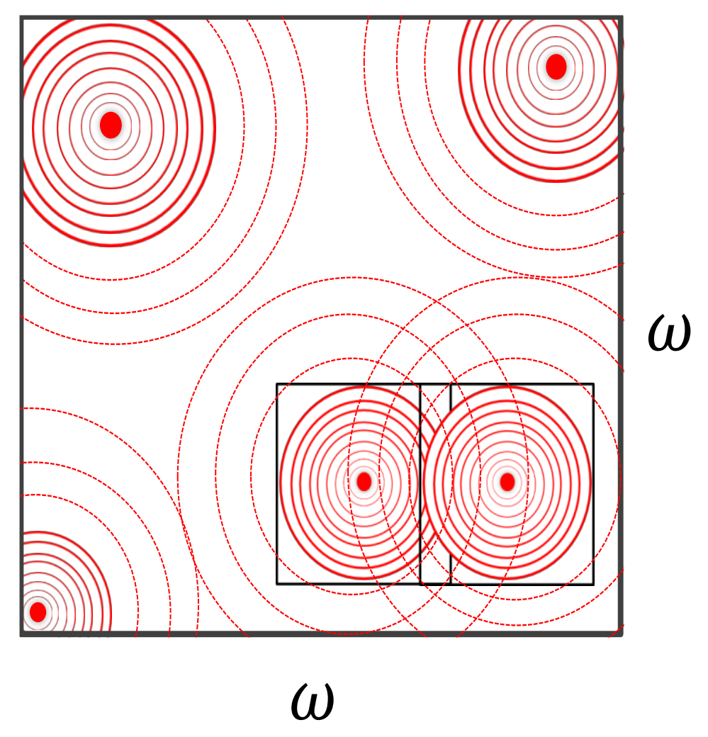

Fig . 5 Schematic view of ion tracks passing through a cell nucleus of a simplified square area ω^2~25µm^2 (average area of a human lymphocyte nucleus). Two ion tracks are close enough to overlap.

We can define repair coefficient RC , which corresponds to the probability of repair and is described by the relation:

$$RC = \frac{Y' - Y}{Y'}$$

The aberration yield Y observed under microscope is the result of the DNA damage processing (repair) and Y' corresponds to the number of aberrations if no repair mechanisms would act.

In the model, simple linear *RC* dependence assuming may be applied (blue line, figure 6) :

$$RC = RC_0\left(1-\frac{D}{D_0}\right)$$

Comparing the above equation with the *RC* definition

$$RC_0\left(1-\frac{D}{D_0}\right) = \frac{Y'-Y}{Y'}$$

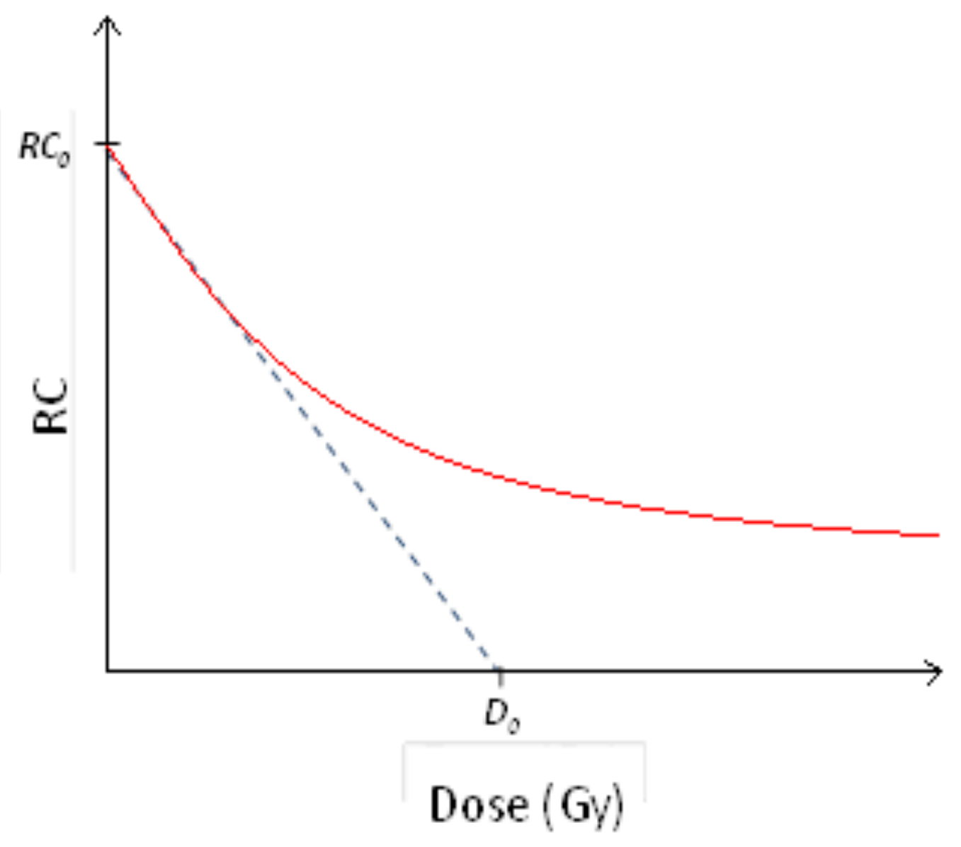

Fig. 6 Linear dependence of the repair coefficient on the radiation dose . Blue dotted line represents the model used to derivate biological β/α ratios. Red line represents real situation of saturation of repair mechanisms after certain dose.

the dose response curve may be obtained

$$Y = (1-RC_0)\alpha_{phys}D + \frac{RC_0}{D_0}\ \alpha_{phys}D^2$$

and the corresponding α_{biol} and β_{biol} parameters and their ratio can be determined:

$$(\beta/\alpha)_{biol} = \frac{RC_0}{D_0(1-RC_0)}$$

The highest repair coefficient RC_0 represents the situation when the microscopic dose deposited by charged particles is in the vicinity of zero. If human lymphocytes are taken into account RC_0 depends only on an individual response and conditions of a given donor. In the case of chromosome aberrations the *RC* value decreases up to given critical point at which efficiency of the repair saturates (see figure 6 red line).

If we assume, that the interaction between ionization sites of neighboring tracks occurs, the initial damage yield *Y'* may be fitted by second order polynomial curve:

$$Y' = \alpha_{phys}\,D + \beta_{phys}\,D^2$$

Experimentally obtained aberration yield *Y* which comprises the result of DNA repair and repair coefficient *RC* satisfies the relation

$$Y = Y'\,(1-RC) = \left(\alpha_{phys}\,D + \beta_{phys}\,D^2\right)\left(1 - RC_0 + \frac{RC_0}{D_0}\,D\right)$$

Under the condition that $\frac{RC_0}{D_0} \ll 1$ and $\beta_{phys} < \alpha_{phys}$, the aberration yield the relation describing *Y* reads as follows:

$$Y \cong (1-RC_0)\alpha_{phys}\,D + \left(\frac{RC_0}{D_0}\,\alpha_{phys} + \beta_{phys}\,(1-RC_0)\right)D^2$$

Expressions standing next to the dose and the square of the dose represent experimentally obtained response curve parameters - α and β, respectively. The ratio of these parameters leads to the relation

$$(\beta/\alpha)_{exp} = \frac{RC_0}{D_0(1-RC_0)} + \frac{\beta_{phys}}{\alpha_{phys}}$$

Finally, we get the relation combining biological and physical processes leading to the formation of LQ shape of the dose-response curves of chromosome aberrations:

$$(\beta/\alpha)_{exp} = (\beta/\alpha)_{biol} + (\beta/\alpha)_{phys}$$

Table 2	**R$_{min}$ (nm)**	**R$_{max}$ (µm)**	**R$_{phys}$ (nm)**	**R$_{exp}$ (nm)**	**(β/α)$_{exp}$** (*Gy* $^{-1}$)
150 MeV protons	5.8	93	23.02	318.±25.	1.9±0.4
SOBP protons	2.32	8.14	9.65	287.±28.	0.72±0.13
^{12}C ions	6.56	126.9	29.86	620.±47.	0.26±0.04
^{60}Co γ rays	-	-	-	175.±30.	1.6±0.5
^{11}B ions	2.55	9.65	10.95	-	-

Summary

- ➢ Simple expression for physical effective radius of overlapping ion tracks makes it possible to determine the track radii which would be necessary to explain experimentally observed $(\beta/\alpha)_{exp}$ values.
- ➢ The physical radii are much smaller than the experimental ones. Therefore, the main effect contributing to the LQ model should be a biological repair mechanism.
- ➢ We assumed a simple dose dependence of the repair coefficient as used for survival curves, which provides the quadratic term in the LQ model

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