

Mathematical Models of Radiation-Induced Mitotic Delay: Time Course Analysis and Statistics of Lesions

E. Gudowska-Nowak^{1,3}, A. Kleczkowski², G. Kraft³, E. Nasonova^{3,4}, S. Ritter³, M. Scholz³

1. Marian Smoluchowski Institute of Physics, Jagellonian University, Kraków (Poland)

2. King's College, University of Cambridge, Cambridge (UK)

3. Gesellschaft für Schwerionenforschung, Darmstadt (Germany)

4. JINR, Dubna (Russia)

Abstract

Detailed investigations of high and low LET radiation induced chromosome aberrations in various mammalian cell lines have shown that the registered yield of aberrations depends on cell cycle progression delays.

The effect of radiation on the cell kinetics can be analyzed in terms of kinetic growth models. The method yields the number of aberrant cells and the number of aberrations as totals obtained after integration over given time-interval.

KEYWORDS: Growth models, radiation-induced mitotic delay, yield of aberrations.

1. Introduction

Irradiation of synchronized cell population leads to cell cycle delays and desynchronization; both effects are known to increase with LET. Changes in the cell cycle progression affect visibility of radiation induced chromosome damage and complicate the determination of meaningful RBE values. As recently shown [1-3], traditional methods of analysis based on single sampling time lead to underestimation of radiation effects and RBE values depending on the sampling time. The approach based on time-course of aberrations allows a better analysis of experiments [1, 3] using extremely different radiation and consequently different cell cycle perturbations. Statistical analysis of data is based in such a case on fairly general growth models known in population dynamics.

2. Mathematical model and analysis of experimental data

The problem can be posed as a growth of the population of aberrant cells N with a time-dependent 'reaction rate' $m(t)$, which represents the mitotic index at a given sampling time.

$$N \xrightarrow{m(t)} 2N \quad (1)$$

The measured mitotic indices of a synchronized cell population are corrected for proliferation, so that the integral of $m(t)$ over the time span of the first cycle is normalized to 1. The above kinetic scheme can be analyzed in terms of the Gompertz equation

$$\frac{dN}{dt} = m(t)N \quad (2)$$

with a solution given by

$$N(t) = N_0 \exp\left(\int_0^t m(\tau) d\tau\right) \quad (3)$$

where \hat{I}_0 standó for thå initial cell number. The method can be easily reframed in terms of an iterative procedure, where tõe increase in cåll numåer from time step $i - 1$ to time i is governed by the equation $N_i = N_{i-1}(1 + m_i)$. Figure 1 shows an example of the 'kinetic rate' representing fraction of mitotic cells passing through mitosis. Iterated fluxes of aberrant and undamaged cells reconstructed from the growth equation (2) are shown in Figure 2 demonstrating visible mitotic delay of cells carrying aberrations.

Integration of fluxes of aberrant cells over the time interval of the first cycle (from about 10 to 16 hrs after irradiation, cf. Figure 1) leads to the total number or aberrant mitoses with respect to the initial cell population. The same kinetic scheme can be used to estimate total yield of aberrations per N_0 cells of the initial population. If the reconstructed growth is carried with a weighted mitotic index $m_i^* = m_i N_i / N_0$, covering the whole time span of the first mitosis and given all cells passed the mitosis, the cell number at the end of that interval should double. The loss of cells can be thus visualized by differences in the number of control cells which completed first mitosis *versus* the relevant number of aberrant cells completing the first cycle.

3. Limitations of the method

The accuracy of the method depends strongly on the number of sampling times in collected experimental data. If cell samples are not continuously harvested, the procedure can lead to an unprecise estimate because the minima or maxima of the $m(t)$ function could be missed. This can be easily clarified by

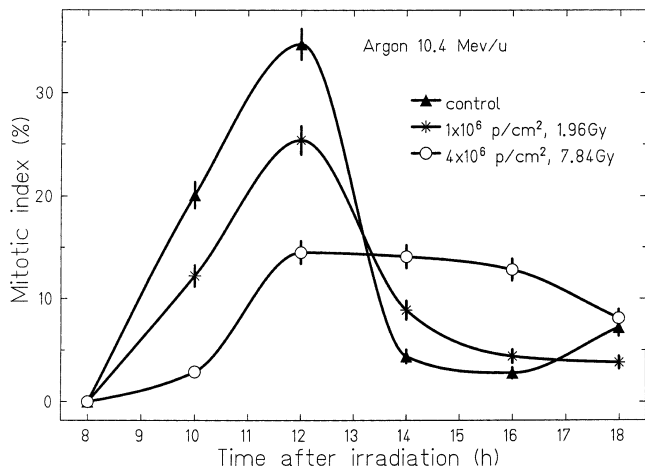


Fig. 1 – Mitotic indices $m(t)$ for 2h colcemid accumulation periods following irradiation of V79 G_1 cells with 10.4 MeV/u Ar ions. Experimental data from ref. [3].

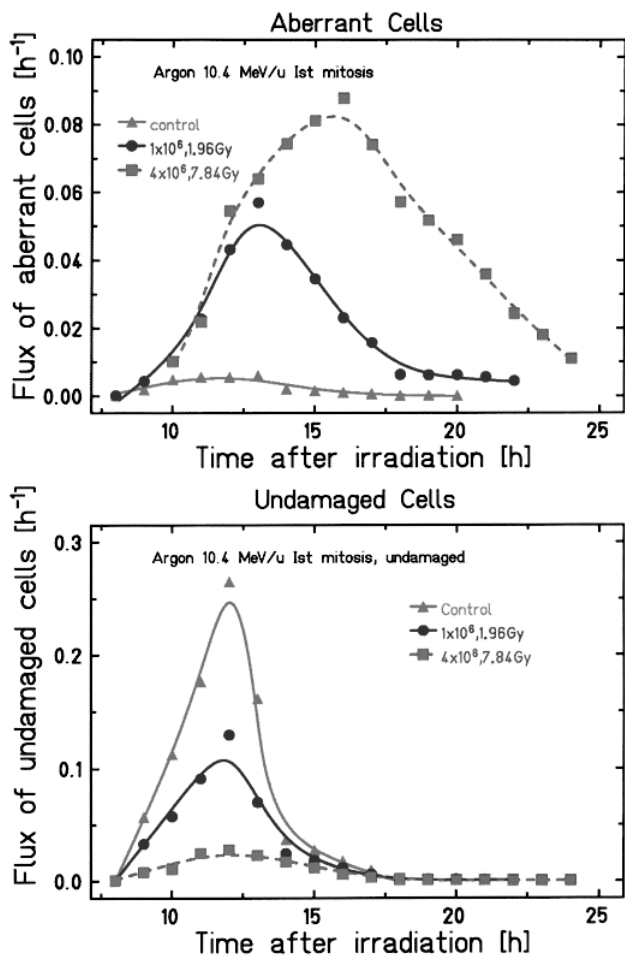


Fig. 2 – Passage of undamaged and aberrant cells through first mitosis after irradiation with 10.4 MeV/u Ar ions (LET: 1226keV/ μ m, experimental data from [3]).

assuming the model of the kinetic rate $m(t)$ based on the theory of point processes, for which $m(t)$ represents the distribution of intervals between two events. For intervals being sums of α independent,

exponentially distributed random variables $t = t_1 + t_2 + \dots + t_\alpha$ having common parameter β , function $m(t)$ is a gamma distribution density:

$$m(t) = \frac{\beta^{\alpha+1}}{\Gamma(\alpha+1)} \exp(-\beta t) t^\alpha \quad (4)$$

To model uncertainty in the kinetics, let us assume that the rate parameter β in the gamma distribution is sampled from a normal distribution with the mean 0.5 and the relative dispersion of $\pm 20\%$. The shape parameter α is fixed at 5. Figure 3 shows that the errors in the parameter β (or, effectively in function $m(t)$) propagate through the solution (3) and in the finite time interval can result in various ‘plateau’ levels characterizing fraction of cells which completed mitosis.

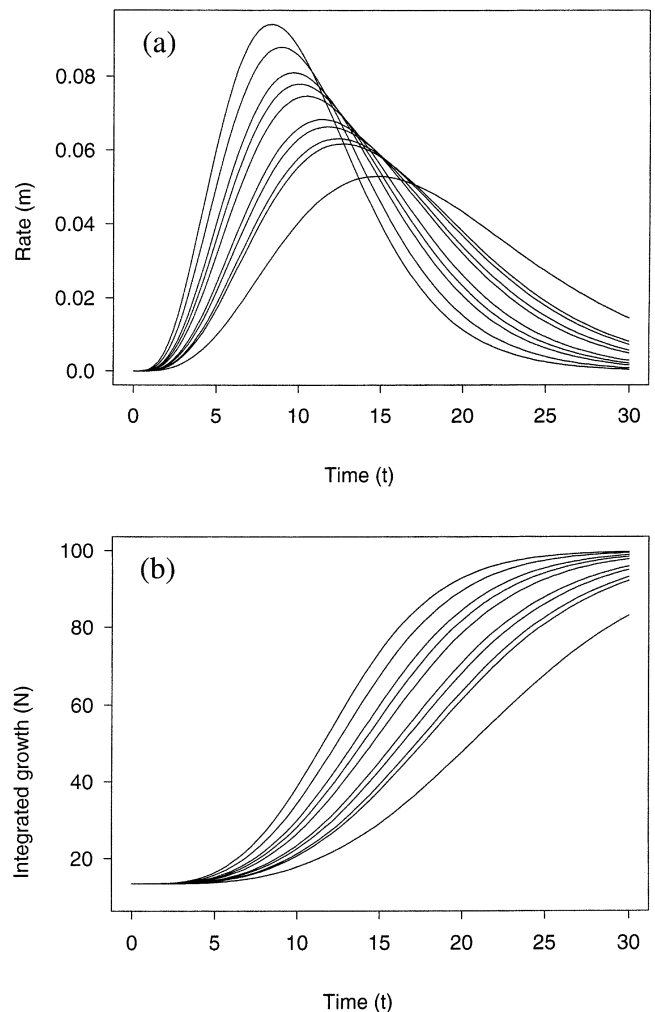


Fig. 3 – Variation in the kinetic rate (top graph) and in the percentage of damaged cells undergoing mitosis. The rate parameter is normally distributed with a mean value 0.5 and the relative dispersion of $\pm 20\%$; arbitrary time units.

4. Conclusions

Distinct differences in the cycle progression of damaged and intact cells (Fig. 1) demonstrate the need for analysis of chromosome aberrations based on multiple sampling times. The approach using the time-

course of aberrations allows a better analysis of experiments [1, 3]. The formalism yields correct 'totals' of aberrations and aberrant cells, gives suitable estimation of lost cells from the reconstructed growth and provides better control of cycle delays for cells carrying radiation-induced damage. The method shows that only integrated number of aberrations and aberrant cells will result in reliable estimates of RBE.

Acknowledgements

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