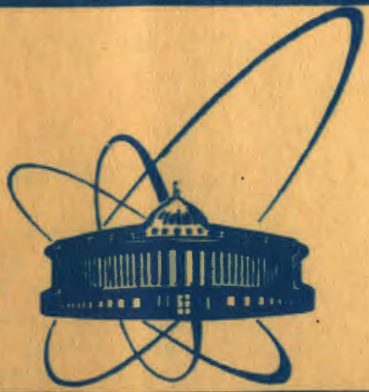

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RADIOBIOLOGICAL MECHANISM IN CELLS.

Model Analysis of DSB Formation and Their Repair

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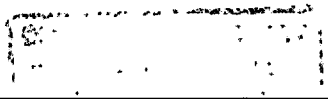
1. INTRODUCTION

Last years have provided us with a series of new results which have brought the radiobiology from less or more qualitative and phenomenological level to the study of more exact problems, concerning radiobiological mechanism in a cell. This progress has been accompanied by a rather substantial change in interpreting the shoulder on survival curves. In the past practically any theory of radiobiological mechanism started from the assumption that the shoulder is given already in the course of formation of primary lesions in a cell (see, e.g., ref.[1]) even if a nature of these lesions was not known. It was assumed that they are formed mostly in two quite independent steps (at least for low-LET ionizing particles).

Now, there exists a common convinction that the primary lesions must be identified as double-strand breaks (dsb) of DNA molecules in a cell nucleus; and it has been also found for many different cell types that the dsb number is proportioval to the absorbed dose. The shoulder on a survival curve should be, therefore, related to dsb repair (see, e.g., refs. [2,3]).

Even if we can be practically sure that the dsb are main lesions responsible for cell inactivation, it is impossible to answer the question whether other types of damages do not contribute significantly to a final effect. The problem is so comlex that it can be hardly solved without the help of detailed mathematical models, which would describe all characteristics not only of dsb formation but also of their repair. Only such a model can help to throw more light on the problem of what is a causal relation between dsb number in a cell and its inactivation and to what extent other damages are contributing.

As the first step to this goal we would like to find a mathematical model of dsb repair, which would be able to express a repair rate for different levels of absorbed dose or of average population damage. We will start from the experimental data published in ref.[3] for one type of yeast cells. This paper presents dose dependence of dsb number at different time after irradiation when the cells were held in non-growth conditions. These data show not only that the dose dependence measured immediately after irradiation is linear, but that approximately after 3 days the dsb number does not further diminish even if repair ability of the solution is not exhausted.



The last curve must be, therefore, related to irreparable dsb which occur together with other reparable lesions. In the next paragraph we will deal with a mathematical model which can cope with such a situation.

2. MATHEMATICAL MODEL OF REPARABLE AND IRREPARABLE dsb

Let N_c be the number of different chromosomes for a given cell type, and N - the total number of critical sites in one set of such chromosomes. That means a diploid cell contains $2N_c$ chromosomes with $2N$ critical sites. Let us assume further that dsb formation is characterized by the quantity r_d which determines a mean number of dsb corresponding to one critical site when the dose D is applied to. It follows from the mentioned linear dose dependence that one can write

$$r_d = \rho_d D, \tag{1}$$

where ρ_d characterizes both radiation properties and some other conditions (e.g., oxygen content a.s.o.).

The number of all dsb formed during irradiation is then given by

$$n_d = 2N p_d, \tag{2}$$

where

$$p_d = 1 - \exp(-r_d) \tag{3}$$

is the probability that at least one dsb if formed in a given critical site (we assume that the distribution of dsb numbers follows the Poisson law with the mean value r_d); it is, however, possible to write

$$p_d \simeq r_d$$

in all experimental data which will be analysed here.

In agreement with ref. /2/ we will assume that the irreparable dsb are formed if two homologous sections in two homologous chromosomes are damaged, since in such a case a pattern for repair is lost. Let us assume further that the length of such a section is given by N_h critical sites. Then the mean dsb number corresponding to this region equals

$$r_h = p_d N_h \tag{4}$$

and one can write for the probability that at least one dsb is formed in it,

$$p_h = 1 - \exp(-r_h). \tag{5}$$

The average number of pair-damaged homologous sections per cell will be equal to

$$r_2 = p_h^2 \frac{N}{N_h}. \tag{6}$$

One obtains then for the number of all dsb in the pair-damaged homologous sections

$$n_i^{(1)} = 2r_2 \frac{r_h}{p_h}, \tag{7}$$

where the fractional factor in the last expression determines the average number of dsb in hit homologous sections. A real number n_i of irreparable dsb can be, however, higher; we must admit that in irreparably damaged chromosomes there will be probably other dsb which will remain irreparable. One can expect that n_i will be between $n_i^{(1)}$ and

$$n_i^{(2)} = N_c p_{h2} r_c / p_c, \tag{8}$$

which is the number of all dsb in irreparably-damaged chromosomes; the individual factors in Eq. (8) are given by

$$r_c = r_d N/N_c,$$

$$p_c = 1 - \exp(-r_c),$$

$$p_{h2} = 1 - \exp(-r_{h2}),$$

where

$$r_{h2} = r_2/N_c$$

is the average number of pair-damaged homologous sections per one chromosome pair.

A real number of irraparable dsb can be then expressed by

$$n_i = (1-\epsilon) n_i^{(1)} + \epsilon n_i^{(2)}, \tag{9}$$

where $\epsilon \in (0,1)$.

3. THE INFLUENCE OF UNHIT POPULATION

If a beam of ionizing particles with a higher LET is applied to, it is commonly assumed that a significant part of cell population remains fully unhit by radiation. In such a case the relation between n_d and n_i given by Eq. (2) and (9) will not correspond to a real situation in a cell. It is necessary to limit oneself to a population part, being at least to some extent hit by the radiation. This can be done with the help of a new parameter x_d, which is defined as a mean dsb number per one cell of a set hit in average by a single particle of a given radiation beam. In other words: Let one beam particle hit b cells on the average and B dsb be formed in total, then the quantity x_d is determined by

$$x_d = B/b.$$

The fraction of the population hit by a dose D can be then determined in the following way: Let us suppose that the average number of beam particles, responsible for the energy transferred by a dose D to a unit volume containing N_V cell nuclei, equals on the average N_D and that the number of nuclei hit by one particle in this volume is n_h. The fraction of hit population will be then given by

$$p_t = 1 - \exp(-n_a), \tag{10}$$

where

$$n_a = N_D n_h / N_V$$

is an average number of hits per one nucleus. As the mean number of dsb formed per one nucleus equals

$$n_d' = n_a x_d,$$

Eq. (10) can be rewritten as

$$p_t = 1 - \exp(-n_d/x_d).$$

The whole approach of the preceding chapter can be used for any radiation type with the following correction for the experimental data

$$n_d' = n_d/p_t, \quad n_i' = n_i/p_t.$$

4. MATHEMATICAL MODEL OF dsb REPAIR

The dose dependences of dsb numbers established in ref. /3/ give the possibility of finding a suitable mathematical description of repair rates for different damage degrees. The dsb number in different periods of time after irradiation could be generally described with the help of the formula

$$n_t = n_i + (n_d - n_i)\, r(t),$$

where $r(t)$ is corresponding monotone repair function with the values $r(0) = 1$, $r(\infty) = 0$.

The given experimental data would require, however, a very complicated parametrization of such a repair function; one can easily see that two components with different repair rates play role in the whole process. It seems more suitable to write

$$n_t = n_i + (n_d - n_x) r_1(t) + (n_x - n_i) r_2(t), \tag{11}$$

where $n_d > n_x > n_i$ and $r_1(t)$ is a fast repair function and $r_2(t)$ – a slow one.

In the following we will use the following parametrization of the individual repair functions

$$r_1(t) = \exp(-\omega t); \tag{12}$$

$$r_2(t) = \frac{\rho + 1}{\rho + \exp[(\gamma t)^\eta]}. \tag{13}$$

The quantity n_x will be then defined by

$$n_x = n_i + \xi (n_d - n_i), \tag{14}$$

where $\xi \in (0, 1)$.

5. ANALYSIS OF EXPERIMENTAL DATA

As we have already mentioned our numerical analysis has been based on experimental data represented grafically in Fig. 7 of ref. /3/. Our aim is to determine all free parameters introduced in the model description in the preceding sections so as to reproduce the given data. However, a sufficient agreement can be obtained only if one allows the parameter ξ to be dose-dependent. We have assumed that this dependence can be expressed as

$$\xi = \xi_1 + \xi_2 n_i' + \xi_3 n_i'^2.$$

With the help of an optimization procedure we have obtained the following values of the individual parameters

$\omega = 0.332, \qquad r = 0.035,$

$\rho = 34.3, \qquad \eta = 3.6,$

$\xi_1 \simeq 0, \qquad \xi_2 = -6.3 \cdot 10^{-3}, \quad \xi_3 = 2.7 \cdot 10^{-4}.$

The change of the ξ parameter in the given dose interval is represented in Fig. 1. Both the repair functions (fast and slow) are shown in Fig. 2. We have also allowed the parameters defining the repair functions to depend on n'_i; only an insignificant dose dependence has been obtained.

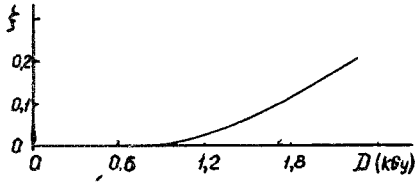
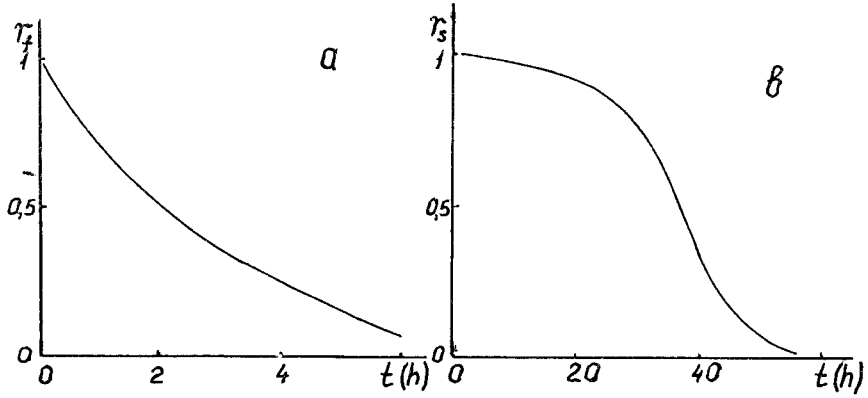


Fig. 1. The dose dependence of the parameter ξ.

Fig. 2. The time dependences of fast (a) and slow (b) repair functions.



The values of the other free parameters for the given cell type are the following

$N_h = 4830,$

$\rho_d = 2.23 \cdot 10^{-6}\ \mathrm{kGy}^{-1}, \qquad x_d = 169.$

The parameters ρ_d and N_h are strongly related to the values of N_c and N, which have been taken

$N_c = 17, \qquad N = 1.5 \cdot 10^7.$

All the values of free parameters correspond to

$\epsilon = 0.68,$

which means (see Eq. (9)) that a great part of dsb in an irreparably-damaged chromosome are also irreparable even if they do not lie in pair-damaged homologous sections. Only a smaller part of such dsb can repair.

It follows from our analysis that the length of a homologous section, responsible for creation of irreparable dsb, is equal approximately to 1/200 of the average chromosome length.

From the data given in Fig. 7 of ref.[3] we have also estimated the standard deviations for individual dose values and determined the χ^2-value of the given fit; we have obtained

$\chi^2 \simeq 40.$

The relatively large value of the quantity x_d for electrons is rather surprising. We must, however, take into account that cells with very small number of dsb can repair their damages so quickly that the repair is finished before any measurement could start. The given value of x_d should be, therefore, related mainly to track ends of secondary electrons the range of which corresponds to a cell-nucleus dimension. It is necessary to compare it with values which will be obtained with the help of some microscopic theory of energy transfer and physico-chemical processes which start in a cell after radiation impact.

6. CONCLUSION

In the present analysis we have made two simplifying assumptions: First, we have divided all dsb into two different groups, one with a fast repair and the other with a slower one. It has been shown that this division is defined by the parameter ξ, which depends on an average damage of the whole population.

The other assumption consists in a description of repair rates by two functions applied always to the whole given part of the population. We have found these functions to be practically damage-independent. One must, however, admit that the repair rates in individual cells can differ rather significantly (even in each of the mentioned parts) as they probably depend on a damage degree of each single cell. The fact that both our functions are practically dose-independent can be taken then as

a sign that any beam particle creates few dsb in a great number of cells; the slow repair should be related, however, to the part of the cells hit by track ends of secondary electrons (i.e., to the cells with a substantially greater number of dsb).

The given orientation analysis shows that the proposed mathematical model can help in solving some important problems of radiobiology. It can be easily extended to the results concerning the survival ratios in different times after irradiation. A corresponding model analysis will be presented in the next article.

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Механизм воздействия излучения на клетки. Модель образования и репарации двунитевых разрывов ДНК

Экспериментальные данные для дрожжевых клеток [3] проанализированы с целью установления некоторых особенностей механизма, ответственного за образование нерепарабельных двунитевых разрывов ДНК. Предложена также математическая модель репарации двунитевых разрывов в условиях, препятствующих росту клеток.

Работа выполнена в Лаборатории ядерных проблем ОИЯИ.

Сообщение Объединенного института ядерных исследований. Дубна 1982

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E19-82-786

Radiobiological Mechanism in Cells. Model Analysis of DSB Formation and Their Repair

The experimental data obtained recently in [3] for a kind of yeast cells have been analyzed with the aim of establishing some features of the mechanism responsible for formation of irreparable dsb. A mathematical model of dsb repair in non-growth conditions has been proposed, too.

The investigation has been performed at the Laboratory of Nuclear Problems, JINR.

Communication of the Joint Institute for Nuclear Research. Dubna 1982