# Mathematical Model for the Sequential Action of Radiation and Heat on Yeast Cells

Jin Kyu Kim[1,*], Yun Jong Lee[1], Su-Hyoun Kim[1], Mohammad Nili[2], Galina P. Zhurakovskaya[3], Vladislav G. Petin[3]
[1]Korea Atomic Energy Research Institute, Jeongeup, 580-185 Korea
[2]Dawnesh Radiation Research Institute, Barcelona, 08007 Spain
[3]Medical Radiological Research Center, 249036 Obninsk, Kaluga Region, Russia
E-mail: jkkim@kaeri.re.kr

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## Introduction

It is well known that the synergistic interaction of hyperthermia with ionizing radiation and other agents is widely used in hyperthermic oncology [1]. Interaction between two agents may be considered as synergistic or antagonistic when the effect produced is greater or smaller than the sum of the two single responses. It has long be consideredthat the mechanism of synergistic interaction of hyperthermia and ionizing radiation may be brought about by an inhibition of the repair from sublethal and potentially lethal damage at the cellular level [2]. The inhibition of the recovery process after combined treatments cannot be considered as a reason for the synergy, but rather would be the expected and predicted consequence of the production of irreversible damage. On the basis of it, a simple mathematical model of the synergistic interaction of two agents acting simultaneously has been proposed [3]. However, the model has not been applied to predict the degree of interaction of heat and ionizing radiation after their sequential action. Extension of the model to the sequential treatment of heat and ionizing radiation seems to be of interest for theoretical and practical reasons. Thus, the purposes of the present work is to suggest the simplest mathematical model which would be able to account for the results obtained and currently available experimental information on the sequential action of radiation and heat.

## Mathematical Model

An understanding of the reason and magnitude of the interactive effects obtained in this study is important both for practical and theoretical point of view. As was pointed out above, the synergistic interaction of ionizing radiation and hyperthermia is not related with the impairment of the recovery capacity itself and that the observed decrease in the rate and the extent of recovery after combined action of these modalities may be attributed to the increased yield of irreversible damage[10]. This means that the inhibition of the recovery process after combined treatments cannot be considered as a reason for the synergy, but rather would be the expected and predicted consequence of the production of irreversible damage. A simple mathematical model of the synergistic interaction of simultaneous action of heat and other agents has been proposed [3]. It would be of interest to adjust this model to the successive application of heat and ionizing radiation and to demonstrate the ability of the model to describe and interpret the results obtained in this study. The model suggests that the synergistic interaction of ionizing radiation and hyperthermia is expected to result from the additional lethal damage arising from the interaction of sublesions induced by both agents. For concreteness sake, let $N_1$ and $N_2$ be the yield of some hypothetical lethal damages produced by ionizing radiation and hyperthermia, respectively. It might be reasonable to assume that some additional effective damage, responsible for the interaction of these agents, has arisen during the successive action of both modalities. It is natural to suppose that the additional damage may be formed due to the interaction of some sublesions induced by both agents. These sublesions are thought to be ineffective when each agent is applied separately. Let $p_1$ and $p_2$ be the mean numbers of the sublesions that arise for one effective damage induced by ionizing radiation and heat, respectively. Then the number of additional lethal damage ($N_3$) responsible for thermal radiosensitization may be given by

$$N_3 = \min\{ p_1 N_1 ; p_2 N_2 \} . \quad (1)$$

According to this equation, the amount of additional damage is determined by the minimal value of the sublesions produced by ionizing radiation ($p_1N_1$) and hyperthermia ($p_2N_2$). This equation has two parameters ($p_1$ and $p_2$) to be estimated from the experimental data. The whole number of lethal damage ($N_\Sigma$) after combined action will be determined by

$$N_\Sigma = N_1 + N_2 + N_3 = N_1 + N_2 + \min\{p_1N_1; p_2N_2\} \quad (2)$$

The effectiveness of cell radiosensitivity by hyperthermia was characterized in this study by the value of TER which was defined as the ratio of slopeof the survival curves obtained after combined action to that after ionizing radiation applied alone. Inasmuch as the slope is determined by the number of effective damage, we can write

$$TER = \frac{N_1 + N_3}{N_1} \quad (3)$$

Combining equations (1) and (3), one can deduce

$$TER = 1 + \min\{p_1 N_1; p_2 N_2\} / N_1 . \quad (4)$$

If follows from Eq. 4 that if $p_1 N_1 > p_2 N_2$ we have

$$TER = 1 + p_2 N_2 / N_1 . \quad (5)$$

Eq. 5 shows that the value of TER should increase with an increase in $N_2$, i.e. the duration of heat exposure, until the inequality $p_1 N_1 > p_2 N_2$ holds. This prediction is in accordance with the data obtained in this study (Figs. 2, 5). It follows from Eq. 4 that if $p_1 N_1 < p_2 N_2$, we have

$$TER = 1 + p_1 , \quad (6)$$

i.e. the value of DMF is constant value from the moment when the inequality $p_1 N_1 < p_2 N_2$ is correct. It was just that was obtained in this study (Figs. 2, 5). In these circumstances, it is to be expected that the duration of heat exposure, at which the plateau of curves depicting the dependence of DMF on the duration of heat exposure begins, should correspond to the following condition

$$p_1 N_1 = p_2 N_2 . \quad (7)$$

This equation shows that this point corresponds to the equal number of sublesions produced by ionizing radiation and heat.

The basic parameters of the model ($p_1$ and $p_2$) can be estimated in the following way. If the inequality $p_1 N_1 < p_2 N_2$ is correct, we have from Eq. (2) that

$$p_1 = (N_\Sigma - N_1 - N_2) / N_1 . \quad (8)$$

On the contrary, if the inequality $p_1 N_1 > p_2 N_2$ holds, we have from Eq. (2) that

$$p_2 = (N_\Sigma - N_1 - N_2) / N_2 . \quad (9)$$

It is well known that in a general presentation cell survival ($S$) is determined by the number of damage by the expression

$$S = \exp(-N) . \quad (10)$$

## Results and Discussion

The proposed model permits the interpretation of the biological data in terms of the numbers of hypothetical sublesions responsible for interaction of heat and ionizing radiation. This method was applied to experimental data presented above. Table 1 includes the estimated basic model parameters and the greatest TER after different conditions of the successive action of ionizing radiation and hyperthermia obtained in experiments and predicted by the model described. A comparison between the theoretically predicted highest values of TER and experimentally determined values shows good correspondence in all cases.

Table 1. The dependence of the basic model parameters ($p_1$, $p_2$) and the greatest TER after different conditions of the sequential action of radiation (γ) heat (H)

| Treatment conditions | | | Model parameters | | The greatest value of TER | |
|---|---|---|---|---|---|---|
| Temp. ℃ | Dose rate, Gy/min | Order of treatment | $p_1$ | $p_2$ | Experiment | Theory |
| 50 | 2 | γ + H | 1.9 | 4.5 | 3.0 | 2.9 |
| 50 | 2 | H + γ | 0.8 | 2.8 | 1.7 | 1.8 |
| 50 | 80 | γ + H | 1.9 | 4.5 | 3.0 | 2.9 |
| 50 | 80 | H + γ | 0.8 | 2.8 | 1.7 | 1.8 |
| 58 | 2 | γ + H | 0.5 | 0.8 | 1.5 | 1.5 |
| 58 | 2 | H + γ | 0.5 | 0.8 | 1.5 | 1.5 |
| 58 | 80 | γ + H | 0.8 | 0.8 | 1.9 | 1.8 |
| 58 | 80 | H + γ | 0.8 | 1.8 | 1.9 | 1.8 |

## Conclusion

In spite of the approximations used in the simplified model considered, the experimental results seem to be in reasonable agreement with the model predictions. The results of this study demonstrate a possibility of reconcilable explanation and prediction of experimental data on the sequential action of heat and ionizing radiation on yeast cells. Inasmuch as the postulates lying in the basis of the mathematical model presented have been formulated in a common sense and concern neither the concrete mechanism of action of the agents applied nor the peculiarities of the biological object tested, one can expect the applicability of the model to predict the effectiveness of interaction of different agents applied sequentially to living cells of various origin.

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