J Korean Med Sci 2001; 16: 283-9
ISSN 1011-8934

Development of Semi-Empirical Model for Radiochemical Reactions

A mathematical model, which represents the radio-chemical reactions in water, was developed to study the effect of the radio-chemical products on cell kiling. The five differential equations were solved using dose rate equation and cell survival as a function of dose was computed. The known chemical rate constants were taken from the literature and unknown constants were determined by curve fitting to an experimental data. Sensitivity studies were performed by varying the rate constants and showed that the yield of H-radical had little effect whereas the change in concentration of OH-radical and direct interaction resulted in significant change on cell survival. The sensitivity studies showed good agreement with the observed effects. In conclusion, we developed a mathematical model that could be used as a means for the estimation of radiation damage.

Key Words : *Free Radicals; Cell Survival; Models Theoretical*

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Received : 16 October 2000
Accepted : 15 February 2001

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INTRODUCTION

The effect of ionizing radiation on cell killing has been extensively observed and various empirical relations have been used to describe the experimental findings. These include single-hit/single-target, single-hit/multi-target, and linear quadratic models (1-3). Additionally, the effects of radiosensitizer on cell killing such as hyperthermia and oxygen have been studied rigorously (4-10). These studies have produced both experimental and clinical evidences for the effectiveness of the radiation on cell killing and the treatment of cancer. Nevertheless, there are few analytical tools available to describe the effects of radiation in biological systems. One option consists of rigorous, sophisticated software codes that are based on techniques such as Monte-Carlo or discrete ordinates. Another option is the calculation of dose based on estimation of absorbed energy. As an interim tool, the fast running mathematical model of dynamics of radiation interaction in tissue might be of use. More importantly, there is no such mathematical model to describe the combined effects of radiation and heat.

A model had previously been developed at the MIT Nuclear Reactor Laboratory that described the interaction of radiation in tissue based on chemical effects of radiation (11). This model was developed by writing equations in space, time, and where appropriate, energy that described both indirect and direct damages to DNA. These equations were then simplified by the application of standard techniques from reactor physics analysis that allowed the reduction of these equations to ordinary time-dependent ones. A limitation of this model was that it simplified the known chemical effects of radiation by treating all indirect actions as a result of a single agent. In addition, this model did not include the effect of oxygen, which is known to be an important radio-sensitizer on cell killing. The present study modified this model to include all known chemical reactions explicitly.

The model is admittedly semi-empirical in that while some of the rate constants as well as other parameters adopted in the equations were taken from the data reported in the literature, others were determined by curve fitting to the experimental data. Therefore, the benefit of this model lies in the fact that it can provide a means to correlate the experimental observations. It reproduces the observed effects and can be used to estimate the sensitivity of these effects in regard to each chemical reaction yield and chemical rate constant. As such, this model may help the investigators to tailor their experiments to identify factors that might provide a biological explanation.

MATERIALS AND METHODS

A schematic diagram of the radiation interaction in a biological system is illustrated in Fig. 1 (12). The radiation interacts physically with biological tissue in less than

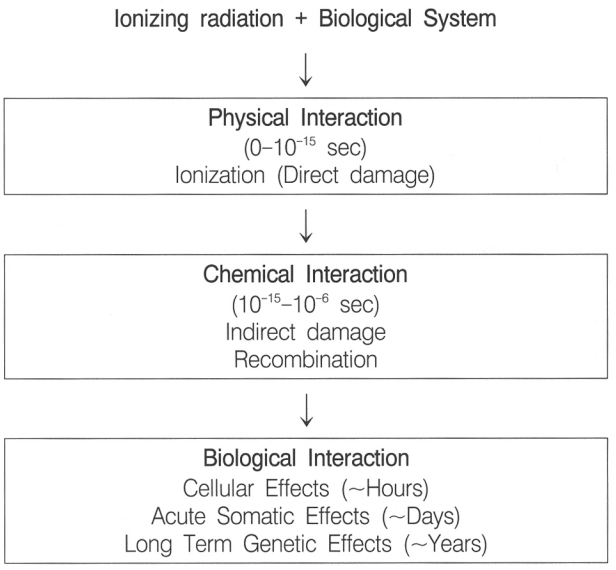

Fig. 1. Time sequence of the effects of radiation on a biological system.

10^{-15} sec. The excited or ionized molecules are produced at this stage. The chemical interactions, which include the production of damaged organic molecules by radicals and the recombination of radicals to form peroxide and water, follow in subsequent 10^{-6} sec. The biological effects occur in a time scale of hours to years. These effects include cell killing, acute somatic effects such as the gastrointestinal symptoms, and genetic effects (13, 14). In particular, the effect of the chemical rate constants on cell survival was modeled. The radiochemical reactions in water and organic molecules are summarized below (14).

(G1)	$Radiation+H_2O$	$\rightarrow H\cdot$	(1)
	$Radiation+H_2O$	$\rightarrow e^+ + H \rightarrow H\cdot$	(2)
(G2)	$Radiation+H_2O$	$\rightarrow OH\cdot$	(3)
(G3)	$Radiation+RH$	$\rightarrow R\cdot$	(4)
(R1)	$OH\cdot+OH\cdot$	$\rightarrow H_2O_2$	(5)
(R2)	$H\cdot+H\cdot$	$\rightarrow H_2$	(6)
(R3)	$OH\cdot+H\cdot$	$\rightarrow H_2O$	(7)
(R4)	$OH\cdot+RH$	$\rightarrow R\cdot+H_2O$	(8)
(R5)	$H\cdot+RH$	$\rightarrow R\cdot+H_2$	(9)
(R6)	$H\cdot+R\cdot$	$\rightarrow RH$ (Repair)	(10)
(R7)	$H\cdot+O_2$	$\rightarrow HO_2\cdot$	(11)
(R8)	$HO_2\cdot+HO_2\cdot$	$\rightarrow H_2O_2+O_2$	(12)
(R9)	$RH+H_2O_2$	$\rightarrow R\cdot$	(13)
(R10)	$RH+HO_2\cdot$	$\rightarrow R\cdot+H_2O_2$	(14)
(R11)	$R\cdot+O_2$	$\rightarrow RO_2\cdot$ (damage fixation)	(15)
(R12)	$RO_2\cdot+RH$	$\rightarrow R\cdot+RO_2H$	(16)

In these reactions, G1, G2, G3 represents yield of H-radicals, OH-radicals and damaged organic molecules (R•), respectively. The rate constants for each of the reactions are described as symbol R. The equations (11), (12), (14), (15), and (16) were not included in the calculation because the goal was to study the effects of rate constants in the absence of oxygen and to provide an analytical model in describing cell survival at the chemical stage of radiation interaction with matter.

The development of this model begins with a consideration of indirect effects. Five differential equations were written as functions of space, time, and energy that represent indirect effects of radiation. These equations were then simplified to a function of time only by using mathematical methods from reactor physics such as one group theory (11). These five differential equations were based on the chemical reactions identified above.

$$\frac{d[OH\cdot]}{dt} = G_2\phi - R_1[OH\cdot]^2 - R_4[OH\cdot][RH] - R_3[OH\cdot][H\cdot] \quad (17)$$

$$\frac{d[H\cdot]}{dt} = G_1\phi - R_5[H\cdot][RH] - R_6[H\cdot][R\cdot] - R_2[H\cdot]^2 - R_3[OH\cdot][H\cdot] \quad (18)$$

$$\frac{d[H_2O_2]}{dt} = R_1[OH\cdot]^2 - R_9[RH][H_2O_2] \quad (19)$$

$$\frac{d[R]}{dt} = -G_3\sigma_r[RH]\phi - R_4[OH\cdot][RH] - R_5[H\cdot][RH] + R_6[H\cdot][R\cdot] - R_9[RH][H_2O_2] \quad (20)$$

$$\frac{d[R\cdot]}{dt} = G_3\sigma_r[RH]\phi + R_4[OH\cdot][RH] + R_5[H\cdot][RH] - R_6[H\cdot][R\cdot] + R_9[RH][H_2O_2] \quad (21)$$

In the equations, ϕ is photon flux (photons/cm^2 sec) and σ_r is the microscopic scatter cross section of organic molecule (RH). Each differential equation indicates the difference between the formation and the removal of a chemical species and hence indicates the change in concentration of that species as a function of time. Cell survival as a function of radiation dose was then computed to estimate the effects of each parameter on cell killing. In the above equations, G1, G2, and G3 represent the number of radicals produced per unit distance and the variables R1 through R12 represent chemical rate constants.

The dose delivered to cells by X-rays was calculated from the following dose rate equation.

$$\text{X-ray: } \dot{D}\text{ose} = [1.6\times10^{-8}]\times E\times\mu_m\times\frac{1}{\rho}\times\phi \quad (22)$$

where $\dot{D}$ose is dose rate (cGy/sec), E is photon energy (MeV), μ_m is energy absorption coefficient for tissue (cm^{-1}), ρ is tissue density (g/cm^3), and ϕ is photon flux (photons/cm^2 sec).

To solve the above equations, the rate constants as

Table 1. The summary of chemical constants used to evaluate the proposed model for the prediction of the cell survival curve

Symbol	Reaction	Constant (cm^3/sec)
R1	$OH+OH \rightarrow H_2O_2$	1.8×10^{-11}
R2	$H+H \rightarrow H_2$	4.1×10^{-11}
R3	$H+OH \rightarrow H_2O$	8.3×10^{-16}

well as the other physical constants should be determined precisely. However, such information is not available in all cases. The chemical rate constants that were taken from the literature are listed in Table 1 (15, 16). A standard human (70 kg) consists of appromately 7×10^{13} cells. Thus, a figure of 1.0×10^{10} cells/cm^3 was used as the initial DNA concentration. In order to determine the flux to be used in the model, the effect of dose rate on cell killing was considered. It is known that exposure at a lower dose rate yields a higher cell survival for the same total dose of low linear energy transfer (LET) radiation (17-19). This is due to the ability of cells to repair the radiation damage at a low dose rate. In order to avoid this effect, a high dose rate of around 100 cGy/min was used for almost all of the experimental data that was reviewed in this study. Studies also showed that there is no dose rate effect if a high dose rate of 100 cGy/min or above is used (20). Based on this value, the flux for x-rays was calculated from the above equations and a flux of 5×10^{10} particles per second was chosen. Other constants that were unknown were obtained by fitting the equations to experimental data (21).

The sensitivity studies were then performed to evaluate the effects of rate constants on cell killing. All known constants were varied by a factor of 5 to 10. In addition to the sensitivity study, a chemical reaction enhancement ratio (CRER) was calculated as follows in order to evaluate the effects of the unknown constants on cell survival in a more quantitative manner:

$$(CRER)_x = \frac{D_0}{D_x}$$

where D_0 is the radiation dose required to produce a given level of cell killing and D_x is the dose required to produce the same level of cell killing when the rate constant was increased by a factor of x.

RESULTS

Table 2 shows the rate constants obtained by fitting the cell survival curves. Because the rate constant for the H and H-radical reaction is faster than that for the OH and OH-radical reaction by a factor of about two, as shown in Table 1, the rate constant for the reaction between H radicals and DNA was assumed to be faster by a factor of two as compared to that between OH radicals and DNA. A similar value for the rate constant between damaged DNA and H-radical was used because the experimental studies showed that there is little or no repair if a high dose rate is used (20). Another reason was that the chemical reaction between H-radical and damaged DNA is not a significant repair mechanism. Rather, a biological repair mechanism is dominant in cell survival (20). Fig. 2 shows the result obtained by solving the above differential equations with the selected constants. With the values chosen, the cell survival curve that was reported experimentally was reproduced.

Table 2. The summary of the fitted rate constants to reproduce the cell survival curves and to perform the sensitivity study

Constants	Reaction	X-rays (250 kVp)
G1 (#/cm)	OH radical yield	0.01
G2 (#/cm)	H radical yield	0.015
G3 (#/cm)	Cell killing by direct effect	0.01
R4 (cm^3/sec)	OH+DNA >> Damaged DNA	5.0×10^{-13}
R5 (cm^3/sec)	H+DNA >> Damaged DNA	1.0×10^{-12}
R6 (cm^3/sec)	H+Damaged DNA >> DNA repair	1.0×10^{-14}
R9 (cm^3/sec)	H_2O_2+DNA >> Damaged DNA	5.0×10^{-13}

The sensitivity studies provided the information about the effects of rate constants on cell survival. The followings are the summary.

Yield of H-radical: There was no significant change in the cell killing as predicted by the model when the yield of the H-radical was increased (Fig. 3A).

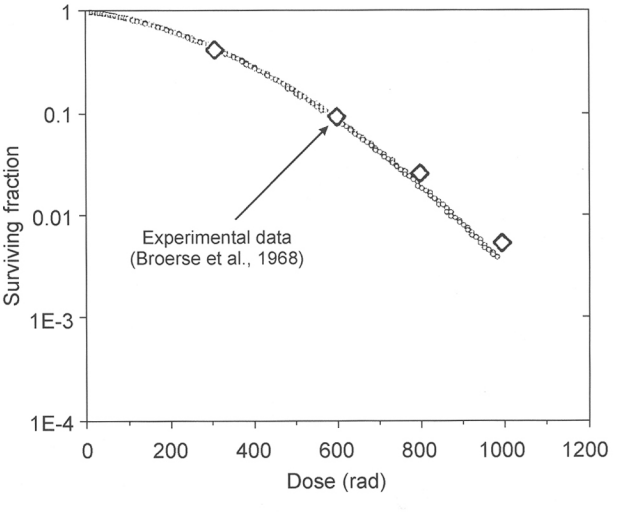

Fig. 2. The cell survival curve fitted with various rate constants for cultured cells of human origin irradiated with 250 kVp X-rays (experimental data were obtained from Broerse et al., 1968, Ref. 21).

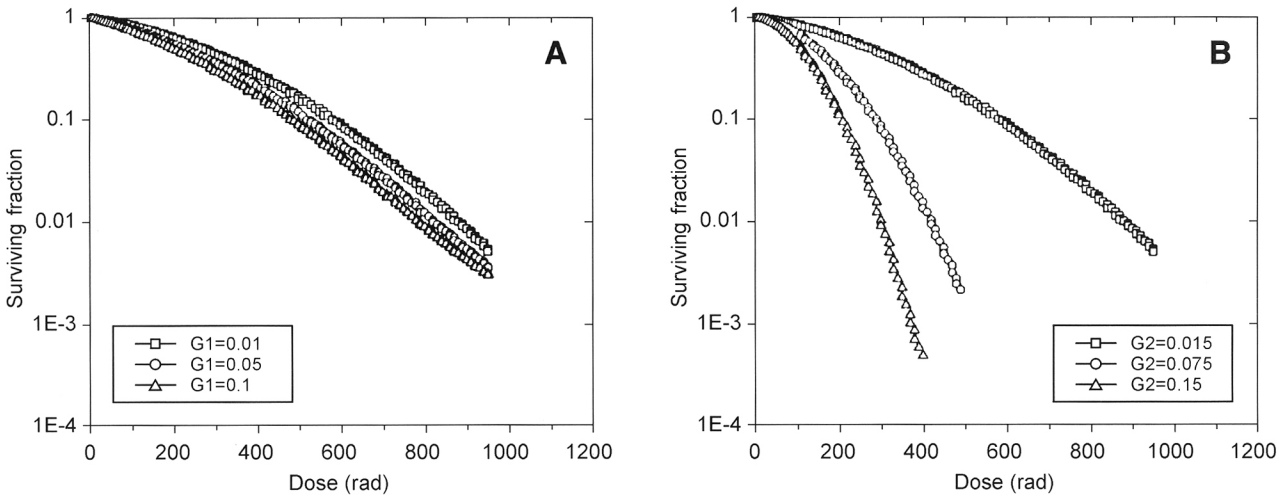

Fig. 3. The cell survival curves obtained by varying (A) H-radical yield and (B) OH-radical yield (open square is the fitted line with experimental data).

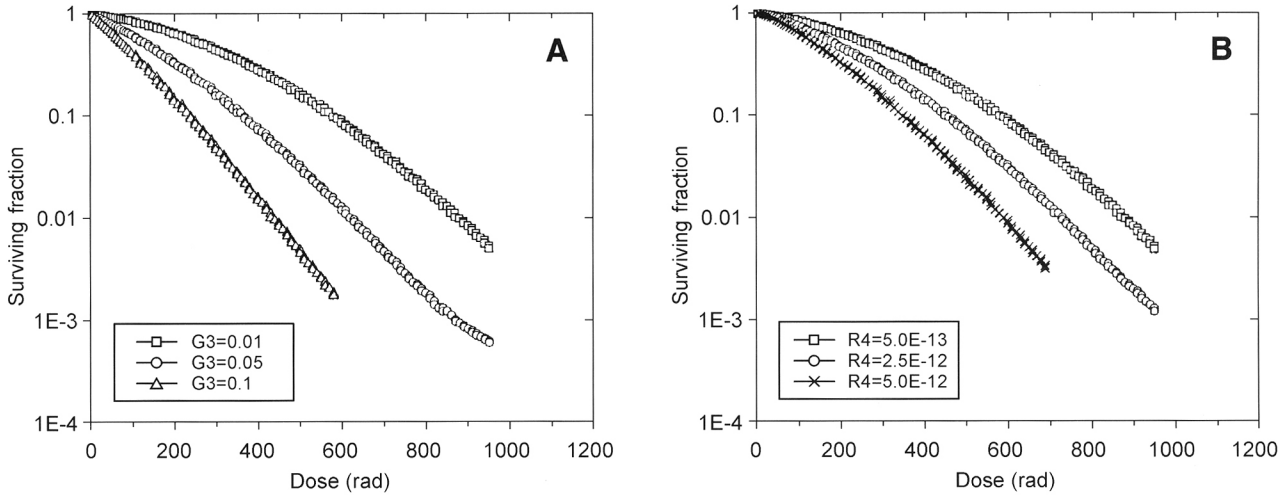

Fig. 4. The cell survival curves obtained by varying (A) damaged DNA yield by direct effect and (B) rate constant R4 for the interaction between OH-radicals and DNA for 250 keV X-rays (open square is the fitted line with experimental data).

Yield of OH-radical: Fig. 3B shows the cell survival curve as a function of OH-radicals. As shown in the figure, there was a significant change in cell survival as the creation of OH-radical increased.

Direct effects of radiation on DNA: Fig. 4A shows cell survival curve as a function of absorbed dose. As the direct interaction between radiation and DNA increased cell survival decreased significantly. This phenomenon can be explained using LET. As known, high LET radiation produces more ionization per unit length and accordingly, it produces more damage than low LET radiation (20, 22-24).

Rate constant between OH-radicals and DNA: There are noticeable increase in cell killing as the rate constant between OH-radicals and DNA increased as shown in Fig. 4B. The dose absorbed by each cell before 37% of the cells are killed was 630 rad, 510 rad, and 400 rad when the rate constants were 5×10^{-13}, 2.5×10^{-13}, and 5×10^{-12}, respectively.

Rate constant between H-radicals and DNA: The model predicted similar trend to that for reaction between OH-radicals and DNA. This might be due to the fact that both radicals promote DNA damage by a similar mechanism (Fig. 5A).

Rate constant between H-radicals and Damaged DNA: The interaction induced the chemical repair of DNA and hence, as would be expected, the change of chemical rate constant did not alter cell survival significantly (Fig. 5B).

Rate constant between peroxide and DNA: According to the literature, peroxide is an active oxidizing agent and

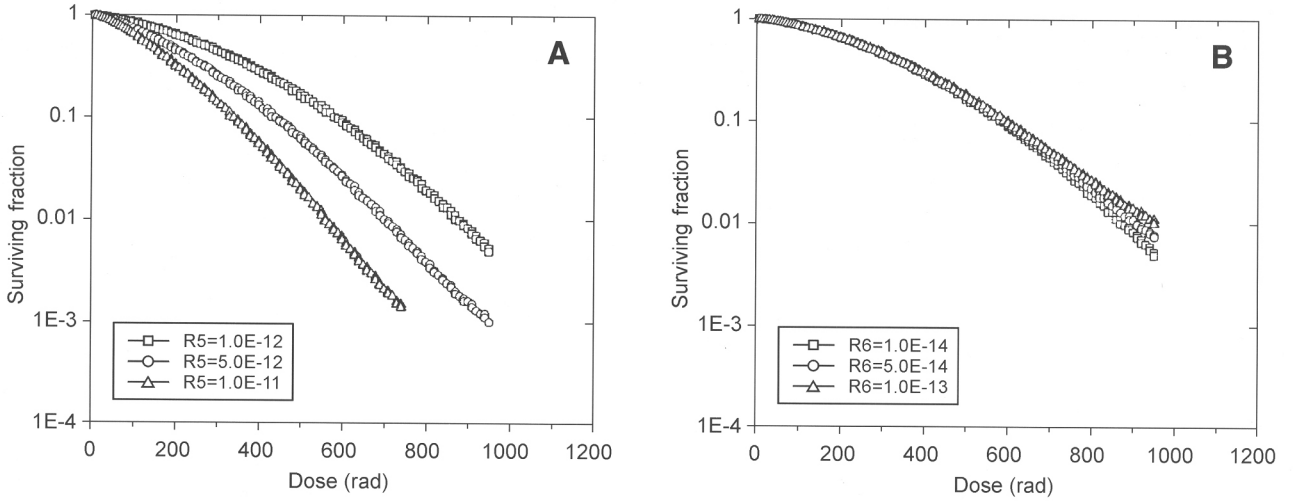

Fig. 5. The cell survival curves obtained by varying (A) rate constant R5 for the interaction between H-radicals and DNA and (B) rate constant R6 for the interaction between H-radicals and damaged DNA for 250 keV X-rays (open square is the fitted line with experimental data).

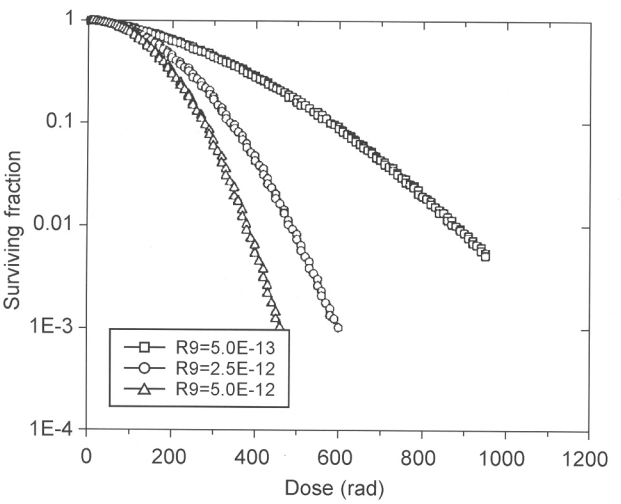

Fig. 6. The cell survival curves obtained by varying rate constant R9 for the interaction between H_2O_2 and DNA for 250 keV X-rays (open square is the fitted line with experimental data).

produces single break through the agency of OH-radical (25-27). Fig. 6 illustrates the effect of peroxide.

The values for the CRER determined from the sensitivity study are listed in Table 3. These values were obtained increasing the known rate constants by a factor of ten. The result shows that, at the highest survival level (60%), maximum CRER of 3.5 minimum CRER of 1 were achieved when yield of damaged DNA and the rate constant between H-radical and damaged DNA were increased, respectively. Considering the overall survival level, cell survival was affected significantly by OH-radical yield and damaged DNA yield. The CRER for the interaction between H-radical and damaged DNA was almost constant over the all range.

Table 3. Chemical reaction enhancement ratio $(CRER)_{10}$

Cell survival (%)	60	35	10	3	1
H-radical yield	1.4	1.3	1.2	1.2	1.1
OH-radical yield	2.4	2.6	2.9	2.9	2.9
Damaged DNA yield	3.5	3.0	2.4	2.1	2.0
OH•+DNA	1.8	1.8	1.7	1.6	1.5
H•+DNA	2.0	1.9	1.8	1.6	1.6
H•+Damaged DNA	1.0	1.0	1.0	1.0	0.9
H_2O_2+DNA	1.6	1.9	2.2	2.3	2.3

DISCUSSION

A mathematical model was developed for the understanding of indirect and direct effects of radiation with matter. The radio-chemical process was modeled by assuming that free-radicals were produced by the interaction of the incident radiation with water and were removed either by peroxide formation or by damage repair process. The enhancement of cell killing in the presence of oxygen which include equations (11), (12), (14), (15), and (16), was not investigated in this study because the goal of this study was to evaluate the feasibility of using the chemical reaction in explaining the cell survival. In order for the reactions (11), (12), (14), (15) and (16) to take place, oxygen has to be present at the time of irradiation and depending upon the concentration of the oxygen and temperature cell survival changes dramatically (28). Therefore the effects of oxygen need to be studied separately.

The examination of the validity of the model was performed through sensitivity studies by varying radical

yields and rate constants. The results of the calculation demonstrated an increase in cell killing as the rate constant increased in all cases, except H-radical yield and the rate constant between H-radical and damaged DNA. As shown in Fig. 3(A), there was little increase in cell killing as the H-racial yield was increase by a factor of 5 and 10. This may be because H-radical fulfills two roles. As described in equation (9), it may promote the creation of damaged DNA. However, once the DNA is damaged, the H-radical may lead to repair as shown by equation (10). This observation is in line with the previous studies that under hypoxic conditions the OH-radical is the major oxidizing species, whereas H-radical acts as a reducing species at the pH of cells (29-31). Due to the competing interaction between DNA damage and damage repair processes by H-radical, there was little effect on cell survival as the rate constants between H-radical and damaged DNA increases. However, the trend was consistent with the experimental data that as the rate constant increased cell survival increased slightly because the reaction represents repair process.

The significant increase in cell survival, as the yield of OH-radical increases, could be explained using the two important processes. First, the concentration of peroxide increases as the number of density of OH-radical increases, which results in more cell killing. Second, the cell killing by the interaction between OH-radicals and DNA increases as the OH-radical yield increases. As a result, the OH-radicals may either cause damage to DNA or combine with each other to form peroxide that in turn, damages DNA. In this study, the former effect was taken into consideration and it was showed that DNA damage is dependent on the rate constant. This result is comparable with the experimental data obtained by Mark et al. (32). The strand break formation of poly(A) and sDNA in aqueous solution as a function of OH radical scavenger was stimulated and it was showed that the single strand break formation increased with a decrease of the scavenger concentration (25). Thus, the model prediction is consistent with the current understanding. However, the degree of enhancement is less than that observed for a change in the yield of OH-radicals (as shown in Fig. 3B and Fig. 4B). This effect indicates that some of the additional OH-radicals would exert their influence through peroxide formation.

By the fact that the interaction between OH-radical and DNA is regarded as direct interaction and high value of CRER is obtained for OH-radical yield and damaged DNA yield, it could be concluded that the direct effect is the dominant mechanism of the damage. However, as cell survival decreases, other effects become increasingly important. At the level of one percent of cell survival, the dominant factors were hydroxyl radical and peroxide followed by the direct effect.

The results for sensitivity study shown above indicated that the predictions of the model were consistent with physical data and demonstrated the feasibility of using the model for radiochemical reactions. Accordingly, it was concluded that the model could be used as a tool to study the effects of radiation on cell killing and possibly the effects of radiosensitizers such as oxygen and hyperthermia. Further work is needed to describe the combined effects of radiation and oxygen to investigate the effects of hyperthermia in cancer treatment.

REFERENCES

1. Coggle JE. *Biological effects of radiation. 2nd ed. London: Taylor and Francis, 1983.*
2. Fox M, Nias AH. *The influence of recovery from sublethal damage on the response of cells to protracted irradiation at low dose rate. Curr Top Radiat Res 1970; 7: 71- 103.*
3. Nias AH, Gilvert CW. *Response of HeLa and Chinese hamster cells to low doses of photons and neutrons. Cell survival after low doses of radiation. Wiley, 1975; 93-9.*
4. Dewey WC, Hopwood LE, Sapareto SA, Gerweck LE. *Cellular responses to combinations of hyperthermia and radiation. Radiology 1997; 123: 463-74.*
5. Gerner EW, Leith JT. *Interaction of hyperthermia with radiation of different linear energy transfer. Int J Radiat Biol Relat Stud Phys Chem Med 1977; 31: 283-8.*
6. Bornstein BA, Zouranjian PS, Hansen JL, Fraser SM, Gelwan LA, Teicher BA, Svensson GK. *Local hyperthermia, radiation therapy, and chemotherapy in patients with local-regional recurrence of breast carcinoma. Int J Radiat Oncol Biol Phys 1993; 25: 79-85.*
7. Wust P, Stahl H, Dieckmann K, Scheller S, Loffel J, Riess H, Bier J, Jahnke V, Felix R. *Local hyperthermia of N2/N3 cervical lymph node metastases: correlation of technical/thermal parameters and response. Int J Radiat Oncol Biol Phys 1996; 34: 635-46.*
8. Lee HK, Antell AG, Perez CA, Straube WL, Ramachandran G, Myerson RJ, Emami B, Molmenti EP, Buckner A, Lockett MA. *Superficial hyperthermia and irradiation for recurrent breast carcinoma of the chest wall: prognostic factors in 196 tumors. Int J Radiat Oncol Biol Phys 1998; 40: 365-75.*
9. Nishimura Y, Hiraoka M, Akuta K, Jo S, Nagata Y, Masunaga S, Takahashi M, Abe M. *Hyperthermia combined with radiation therapy for primarily unresectable and recurrent colorectal cancer. Int J Radiat Oncol Biol Phys 1992; 23: 759-68.*
10. Rau B, Wust P, Tilly W, Gellermann J, Harder C, Riess H, Budach V, Felix R, Schlag PM. *Preoperative radiochemotherapy in locally advanced or recurrent rectal cancer: regional radiofrequency hyperthermia correlates with clinical parameters. Int J Radiat Oncol Biol Phys 2000; 48: 381-91.*

11. Bernard JA, Hu LW. *The application of reactor physics methods to the interaction of radiation with matter. Proceedings of the joint international conference on mathematical methods in supercomputing for nuclear applications 1997.*
12. Turner JE. *Atoms, radiation, and radiation protection. McGraw-Hill, 1992.*
13. Sonntag C. *The chemical basis of radiation biology. London: Taylor & Francis, 1987.*
14. Nias AH. *An introduction to radiobiology. New York: Wiley & Sons, 1990.*
15. Ross AB, Mallard WG, Helman WP, Buxton GV, Huie RE, Neta H. *NDRL/NIST solution kinetics database: version 3.0. Gaitherburg: National Institute of Standards and Technology, 1995.*
16. Simonson SA. *Modeling of radiation effects on nuclear waste package materials, PhD Thesis, MIT 1988.*
17. Bedford JS, Mitchell JB. *Dose-rate effects insynchronous mammalian cells in culture. Radiat Res 1973; 54: 316-27.*
18. Elkind MM, Sutton H. *Radiation response of mammalian cells grown in culture: I. Repair of x-ray damage in surviving Chinese hamster cells. Radiat Res 1960; 13: 556-93.*
19. Michaels HB, Hunt JW. *A model for radiation damage in cells by direct effect and indirect effect: a radiation chemistry approach. Radiat Res 1978; 74: 23-34.*
20. Hall EJ. *Radiobiology for radiologist. 2nd ed. London: Taylor and Francis, 1978.*
21. Broerse JJ, Barendsen GW, van Kersen GR. *Survival of cultured human cells after irradiation with fast neutrons of different energies in hypoxic and oxygenated conditions. Int J Radiat Biol Relat Stud Phys Chem Med 1968; 13: 559-72.*
22. Hall EJ, Roizin-Towle L, Theus RB, August LS. *Radiobiological properties of high energy cyclotron-produced neutrons used for radiotherapy. Radiology 1975; 117: 173-8.*
23. Bird RP, Burki HJ. *Survival of synchronized Chinese hamster cells exposed to radiation of different linear energy transfer. Int J Radiat Biol 1975; 27: 105-20.*
24. Buckton KF. *Indentification with G and R banding of position of breakage points induced in human chromosomes by in vitro irradiation. Int J Radiat Biol 1976; 29: 475-88.*
25. Mark F, Becker U, Herak JN, Schulte-Frohlinde D. *Radiolysis of DNA in aqueous solution in the presence of a scavenger: a kinetic model based on a nonhomogeneous reaction of OH-radicals with DNA molecules of spherical or cylindrical shape. Radiat Environ Biophys 1989; 28: 81-99.*
26. Bladier C, Wolvetang EJ, Hutchinson P, de Haan JB, Kola I. *Response of a primary human fibroblast cell line to H_2O_2 senescence-like growth arrest or apoptosis? Cell Growth Differ 1997; 8: 589-98.*
27. Bradley MO, Erickson LC. *Comparison of the effect of hydrogen peroxide and x-ray irradiation on toxicity, mutation, and DNA damage/repair in mammalian cells. Biochim Biophys Acta 1981; 654: 135-41.*
28. Alpen EL. *Radiation Biophysics. 1st ed. New Jersey: Englewood Cliffs, 1990.*
29. Lett JT. *Double strand breakage in DNA and cellular radiation sensitivity: linear energy transfer and the oxygen effect. In: Simic MG, Taylor KA, Ward JF, von Sonntag C, editors. Oxygen radicals in biology and medicine. New York and London: Plenum Press, 1988; 418-28.*
30. Dertinger H, Jung H. *The action of ionizing radiation on elementary biological objects. New York: Molecular Radiation Biology Heidelberg Berlin Springer-Verlag, 1970.*
31. Pryor W. *Free radical reactions and their importance in biochemical systems. Fed Proc 1973; 32: 1862-9.*
32. Loyd DC, Purrott RJ. *Chromosome aberration analysis in radiological protection dosimetry. Radiat Prot Dosime 1981; 1: 19-27.*