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Modelling Radiation Health Effects

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1. Introduction

Recent years, assessment of low-dose radiation risk have been of increasing importance in an area of public-health investigation because of an increase in many types of exposures, e.g. medical exposures, exposure of astronauts and the cosmic radiation exposure of aircraft crew, and for the radiation-protection viewpoints.

We still have many outstanding questions on health effects of radiation. Generally, the most demanded question is “how much radiation (dose) produces how much effect?” this is the so-called dose-response relationship (Fig.1), especially at low dose region (BEIR VII phase 2, 2006, UNSCEAR 2006 Report Vol. I, Annex A, 2006).

In general, dose-response relationship at low dose region (almost below 100mSv) have no statistical significance, consequently linear extrapolation from high dose region is used for explanation.

![Dose-response relationship](image)

Fig. 1. Dose-response relationship of radiation effects. In general, cancer incidence is used for the response of radiation dose. Dashed line shows linear extrapolation from high-dose region.
At this point, we had better scientifically define the term “radiation effects”. Well, then what is the radiation effect?

Generally speaking, biological radiation effects can be classified in two basic categories, deterministic effects and stochastic effects depending on radiation dose and exposure time, i.e., deterministic effects are consequences of acute high radiation dose. Examples of deterministic effects include skin erythema (reddening), radiation induced cataract, hair loss, radiation sickness (nausea, vomiting and diarrhoea), sterility and depression of red blood cell formation. These effects are due to cell killing, that is to say, they will occur when the cell killing is large enough to cause functional damage of tissue or organ. Therefore, there is a threshold for deterministic effect. In other words, deterministic effects are associated with intermediate to high dose region and the dose-response relationship is fitted well with linear non-threshold (LNT) model which is derived from epidemiological data, e.g., data from A-bomb survivors (Brenner et al., 2003).

On the contrary, stochastic effects are generally associated with long-term low dose exposures. As the name suggests, stochastic effects are described only by the probability. These phenomena (effects) are primarily many types of cancer. Here, we can now define the health effects of radiation at low dose region as carcinogenesis/tumorigenesis.

2. Radiation health effect problem at a glance

Historically, health effects of radiation exposure, especially by high-dose radiation, became apparent just after the discovery of X-ray (BEIR VII phase 2, 2006). In 1895, Wilhelm Conrad Röentgen was investigating an electrical discharge generated from the various types of vacuum tube. During his experiments, he discovered a fluorescent effect on a small black cardboard screen covering vacuum tube and he thought that this fluorescent effect was a consequence of invisible emissions from his experimental equipment. He named these invisible emissions as X-rays, using the mathematical expression for unknown variable.

After the Röentgen’s discovery of man-made radiation, Henri Becquerel discovered naturally occurring radiation emitted from uranium salts in 1896. He reported this discovery at 1896’s proceedings of the French Academy of Sciences under the title “Sur les radiations émises par phosphorescence”, [on the radiation emitted by phosphorescence], in english. Furthermore, Marie and Pierre Curie succeeded in purification and concentration of uranium ore, pitchblende, and they found polonium. Marie also introduced new term “radio-active”. Thus, both man-made and naturally occurring radiation were discovered within several years in the 1890’s.

Because of the invisibility nature of radiation, unfortunately, many types of adverse health effects of radiation became apparent shortly after these early scientific discoveries. Most of the reported health effects in this period are the acute effects such as redness of the skin (erythema), hair loss, decrease in the number of white blood cells, tumorigenesis, and so on. In fact, many of radiation related researchers or radiologists had slow-healing skin lesions in their hands or even died by radiation induced diseases. The most famous example is the case of Thomas Edison’s assistant, Clarence Dally. During Edison’s development of fluoroscopy which is a machine using X-rays to take radiographs, Edison demonstrated his machine by the contribution of his assistant Dally. Thus, Dally died by tumor which was associated with too much exposure. As a consequence, scientists began to know about the potential of radiation to damage human health.
Finally, in 1915, the British Röentgen Society made probably the first adoption of radiation protection recommendations. Therefore, many international or national organizations for radiation health effects were established to meet the growing interest in the subject. At the early stage of radiation effects studies, the main purpose of study or recommendation was radiation protection for patients from diagnostic medical X-ray exposure and also for radiologists. However, stochastic effects of radiation exposure, particularly at low dose, also began to be recognized, during the first few decades of the twentieth century. In spite of the accumulation of knowledge concerning harmful indications of radiation to human body, biological mechanism for the effects of radiation on human body was still lacking the precise knowledge.

Generally speaking, only epidemiological study is the tool to reveal the long-term stochastic effects of radiation. In fact, we need well-controlled, large number and long-term epidemiological studies to investigate late effects (stochastic effects) of radiation health effects, because the numbers of such stochastic effects are too small to determine statistical significance. Although, there have been a small number of epidemiological studies to satisfy these requirements, we can give examples of such well known studies, A-Bomb survivors of Hiroshima and Nagasaki (Preston, 1998, Brenner et al., 2003), 100 years of British radiologists study (Berrington et al., 2001), study of Chernobyl accident (UNSCEAR 2008 Report Vol. II, Annex D, 2008) and international collaborative study of nuclear workers (Cardis et al., 2007, Thierry-Chef et al., 2007, Vrijheid et al., 2007). Adding to these epidemiological studies base on the “population” of considering subjects, more detailed study of biological radiation effects has started due to the birth of molecular biology, by discovery of DNA’s molecular structure by Watson and Crick (Watson and Crick, 1953). In other words, it was the discovery of molecular structure as a “target” of radiation. It is clear that the study of radiation health effects was changed qualitatively and also quantitatively since the birth of molecular biology. It has been believed that the first target of radiation health effects (carcinogenesis) is DNA.

Currently, there are two major methods to investigate the radiation effects on humans, one is the epidemiology which aims to study population level radiation effects the other is the molecular biology which is intended to clarify the radiation effects at cellular or intracellular level. In general, it is known that carcinogenesis by low dose radiation will start from DNA damage by ionizing radiation. Then, these very small effects will appear on a cellular scale by accumulation of various intracellular biological responses with spending long time and finally grow to the tumor with clonal expansion of cancer cell. Fig. 2 is the known hierarchy of biological mechanisms of radiation effects.

Thus, the biological radiation effects are considered as chain reaction phenomena with a very wide scale; DNA damage (space: $10^{-9}$m and time: $10^{-6}$sec) to the tumorigenesis (space: $10^{-3}$m and time: $10^{5}$sec). This is one of the reasons why study of low dose radiation health effects is difficult (Adams & Jameson, 1980).

From the viewpoint of elucidation of dose-response relationship, we should connect small scale dynamics (e.g. DNA damage) with relatively quite large scale dynamics (e.g. tumorigenesis). As shown in Fig.2, we can see that many “subsystems” exist between DNA damage and tumorigenesis. One simple method to solve the problem is the integration of each subsystem’s dynamics. However, it is easy to plan but it is very difficult to implement. Because of the existence of intrinsic uncertainties originate from their own dynamics in each of the subsystems, integration or connection of subsystems will increase whole system’s uncertainty (Jackson, 1991). This is the unpredictable nature of nonlinear systems.
Fig. 2. Spatiotemporal order of radiation effects. Each event will progress to the tumor in a chain reaction as an arrow in the figure.

There are no other problems like radiation health effects study that has much broader spatiotemporal scale, it has at least twenty-four orders of magnitude in time and about ten orders of magnitude in space. Therefore, this will be a very challenging problem in the field of natural science.

Here, another practical difficulty of the problem is noted. In addition to the scaling complexity mentioned above, there is a statistical significance problem associated with sample sizes in low dose radiation health effects problem. For example, due to the inappreciable cancer incidence or infrequent cellular level effects at low dose radiation exposure, we need a large number of experimental data to detect mutations at low dose in a cell culture system, also huge number of data is needed to distinguish the net radiation effects from naturally occurring one in an epidemiological study, however it is practically difficult to get such a large number of data in both cases. To overcome these difficulties in the low-dose radiation effects’ problem, it is considered a good approach to study the process of carcinogenesis using mathematical model which is based on biological mechanism. Next, we will show some examples of mathematical model approaches.

3. Modelling radiation effects – Dynamical system’s view

As described in the previous section, radiation health effects study has much broader spatiotemporal scale. Here, let us begin our analysis by reducing this broad problem into more simple form. Practically, epidemiological problem concerning the population is going to be statistical problem if it turns out the precise incidence of carcinogenesis for each person. Then, what is the cancer incidence for each person? Tumor will be apparent only when it grows to a certain size however the incidence depends on the accuracy of diagnosis, it may define tumor growth at a certain size as one of the endpoints of this broad problem.
Generally speaking, tumorigenesis is thought to be a multistage process with gradual accumulation of mutations in a number of different genes (Fearon and Vogelstein, 1990). How many mutations are required to transform a single normal cell to a cancer cell? This question still has no answer (Sjöblom et al., 2006). Moreover, most of the combinations of mutations in tumors which taken from patients with same cancer type are almost different (Smith et al., 2002). However, biological pathway that transforms normal cell into cancer cell may not be a single pathway, there are well known three sequential state changes, i.e. initiation, promotion and progression (IPP) (Trosko, 1992). This is a so-called multistage carcinogenesis model. Moreover, it is a conceptual dynamics rather than an actual dynamics. The origin of these three processes is thought to be the result of the damage of the chromosomal DNA and failure of its repair. The initiation is defined basically as irreversible changes to target cell, followed by the gene mutations. The stage of promotion, neoplastic development, is believed to be the consequence of the damage of the specific gene expression, e.g., lipid metabolites, cytokines, so the neoplasms may get the enhancement of cellular growth potential, i.e., they lost the intracellular communication. The last stage progression is thought to be a process that the cell acquires malignancy. Cleary, there are two different scale dynamics in this neoplastic process, one is intracellular change process via mutagenic changes and the other is extracellular change or cell group dynamics via cell-cell or cell-environment interactions. Here we may define, from the viewpoint of dynamical systems, “cancer cell” as the uncontrolled neoplastic cell which is developed by intracellular change and “tumor” as the aggregate of such neoplastic cells. In a clinical definition of cancer, there exists a concept “malignancy” which is based on invasion and metastasis; however, it would be one of the aspects of the tumor growth process. Schematic explanation of tumorigenesis in association with IPP concept is shown in Fig. 3.

![Fig. 3. Schematic explanation of tumorigenesis based on IPP concept.](www.intechopen.com)
This is a reduction from large spatiotemporal scale side, then, initial process is unwired for the purpose of modelling. How does radiation induce cancer? In other words, how does radiation induce mutagenic change in a cell? There are several possible pathways to the DNA damages from radiation. In general, radiation will ionize DNA by direct atomic collisions or by indirect manner, as described below.

When an ionizing radiation passes through a water molecule, ionization of water will occur:

\[ H_2O \rightarrow \cdot H_2O^+ + e^- \]  \hspace{1cm} (1)

then ionized water molecule reacts with another water molecule and produce an hydroxyl radical (\( \cdot OH \)):

\[ \cdot H_2O^+ + H_2O \rightarrow H_3O^+ + \cdot OH \] \hspace{1cm} (2)

or \( \cdot H_2O^+ \) breaks up:

\[ \cdot H_2O^+ \rightarrow H^+ + \cdot OH \] \hspace{1cm} (3)

Ejected electron is trapped by polarizing water molecules and will produce hydrated electron \( e_{aq}^- \):

\[ e^- + nH_2O \rightarrow e_{aq}^- \] \hspace{1cm} (4)

and \( e_{aq}^- \) will produce free radical \( \cdot H \) according to:

\[ e_{aq}^- + H_2O \rightarrow OH^- + \cdot H \] \hspace{1cm} (5)

or

\[ e_{aq}^- + H^+ \rightarrow \cdot H \] \hspace{1cm} (6)

Thus free radicals \( \cdot OH \), \( \cdot H \), and \( e_{aq}^- \) are produced by ionizing water molecules. These free radicals are thought to induce DNA damage indirectly; this is so called indirect action. Over the past decades, numerous studies have been made on the initial process of DNA damage using Monte Carlo track structure method (Nikjoo et al, 2006).

Currently, radiation induced DNA damages are roughly classified into four types, 1) base damage, 2) base release, 3) strand break, and 4) crosslink. Sometimes damage of the DNA is lethal to a cell so various repair mechanisms exist depending on the types of damage. For example, the necessary yields of DNA damage to kill 63% of irradiated cells are known, e.g., 1000 for the single strand break (ssb), 40 for the double strand break (dsb), and 150 for the crosslinks, where the number of lesions per cell per \( D_{37} \), and \( D_{37} \) is dose of 37% survival (BEIR V, 1990). Scientific explanation about the rate of DNA repair needs further investigation. It depends on various factors, including cell type, age of the cell, extracellular environment and also the type of DNA damage. Generally, it is thought that these DNA damages are completely repaired, but sometimes there will be unrepair DNA damages or incorrectly repaired DNA damages, and these progreses of DNA damage will determine the cell fate. On a cell which has a large amount of DNA damage accumulation, senescence or apoptosis may occur. On the other hand, misrepair DNA damage is so-called mutation. It is believed that the accumulation of mutations will induce neoplastic transformation. Schematic explanation of initial process of radiation effects which is concerned with DNA damage and mutation is shown in Fig. 4. As described above, detailed dynamics from DNA
damage to mutation still lacking scientific explanation, it is difficult to make mathematical models; it seems to be dominated by some probability.

![Diagram showing the process of radiation effects](image)

Fig. 4. Simplified schematic explanation of initial process of radiation effects, from DNA damage to mutation.

If tumor growth is set as an endpoint for the radiation health effects study, it is good to consider DNA damage, mutagenesis, carcinogenesis and tumorigenesis as the midpoints of the problem. Moreover, it is appropriate to divide roughly the dynamics into intracellular phenomena and extracellular or cell group phenomena because of the dynamics is thought to be dominated by stochastic in intracellular scale or deterministic over cellular scale. Hereafter, mathematical model of cellular scale are introduced.

4. Mathematical model

In fact, there are not so many mathematical models to investigate radiation induced cancer, but there are many types of mathematical models to study common cancer. Detailed mechanism of carcinogenesis is still not well defined concerning carcinogenesis which is induced not only by radiation but also by other carcinogens. Actually, there are not so many radiation specific effects on cancer; there are no diagnosis methods of radiation specific cancer. One of the radiation specific effects is its penetration to whole human body, or it will only appear as a specific type or character of DNA damages, not in cellular level.

Here, some examples of mathematical model of carcinogenesis are introduced even though most of them are not radiation-specific. However there are many mathematical models of carcinogenesis than radiation specific models, it may be helpful in modelling radiation carcinogenesis.

4.1 Modeling carcinogenesis/tumorigenesis in general

There are several types of mathematical models of tumor growth or carcinogenesis, e.g. simple temporal population based dynamics, models based on diffusion or reaction-diffusion type dynamics, individual cell based models, multi-scale models, and so on (Araujo and McElwain, 2004). These models may be classified into three categories, depending on the mathematical expression of the cell, 1) population based (no spatial structure), 2) spatial model which consider tumor as a one continuous density, 3) individual
or single-cell based models. Adding to this classification, dynamical systems could be classified in two or more categories depending on its status: whether the variable (space, time) is continuous or discrete, whether the process is stochastic or deterministic. For example, reaction-diffusion model which is constructed by partial differential equations is deterministic and continuous, models of Cellular Automata (CA) with some rule are discrete and deterministic. Choice of the variable type and the process in constructing mathematical model is very important and it is dependent on the problem to solve. These are classification based on mathematics of the model. Likewise, the endpoint setting is very important for modelling process, because of the endpoint setting will affect the mathematical modelling strategies, i.e., top-down or bottom-up approaches. For the instance, if the cancer growth or age of cancer incidence is the endpoint to solve then reproducible model construction is the purpose of mathematical modelling. Therefore, constructed models often do not reflect specific biological mechanisms, or rather the model seems to be descriptive. On the contrary, the specific intracellular metabolic network is modeled to see some emergent behavior of considering system, or rather the model seems to be mechanistic. The former is also called top-down approach, the latter bottom-up approach.

Hereafter, some of these models will be introduced shortly. One of the classical models in this subject is Hill’s diffusion based model (Hill, 1928). Hill’s idea is that the diffusion of dissolved oxygen through tissues is an important factor by metabolic process. He did not apply his model to tumor growth explicitly, however his idea affect the later mathematical models of solid tumor growth.

Gatenby and Gawlinski (Gatenby and Gawlinski, 1996) made a simple Reaction-Diffusion based model with continuum cell population for the cancer invasion. They made a hypothesis which based on experimental evidences, that tumor-induced alteration of microenvironmental pH is the important key-role for mechanism of cancer invasion. They use simple reaction-diffusion equations with three field variables, \( N_1(x,t) \), the density of normal tissue, \( N_2(x,t) \), the density of neoplastic tissue, and \( L(x,t) \), the excess concentration of \( H^+ \) ions, where \( x \) is for 1-D spatial coordinate and \( t \) is for time. It should be noted that this model include neither dynamics of early tumor formation, i.e. intracellular genetic changes, nor large-scale morphological features of tumor. That is to say, they modeled only microscopic scale population dynamics at the tumor-host interface. These dynamics can be written as following equations.

\[
\frac{\partial N_1}{\partial t} = r_1 N_1 \left( 1 - \frac{N_1}{K_1} - \alpha_{12} \frac{N_2}{K_2} \right) - d_1 LN_1 + \text{\nabla} \cdot \left( D_{N_1} [N_2] \nabla N_1 \right)
\]  

\[
\frac{\partial N_2}{\partial t} = r_2 N_2 \left( 1 - \frac{N_2}{K_2} - \alpha_{21} \frac{N_1}{K_1} \right) + \text{\nabla} \cdot \left( D_{N_2} [N_1] \nabla N_2 \right)
\]  

\[
\frac{\partial L}{\partial t} = r_3 N_2 - d_3 L + D_3 \nabla^2 L
\]  

The first part in Eq. (1) is growth term of normal tissue based on competitive Lotka-Volterra type equation with competition strength parameter \( \alpha_{12} \) where \( r_1 \) is growth rate of normal tissue, \( K_1 \) the carrying capacity, and the second term \( d_1 LN_1 \) is death rate of normal tissue.
proportional to $L$, and the last part shows cellular diffusion with $N_2$ dependent diffusion coefficient $D_{N_2}[N_2]$. Similarly, the first part in equation of neoplastic tissue growth (2) is growth term of neoplastic tissue with Lotka-Volterra competition parameter $\alpha_{21}$, and second term is also cellular diffusion with $N_1$ dependent diffusion coefficient $D_{N_1}[N_1]$ where $r_2$ is growth rate, $K_2$ the carrying capacity. Finally, equation (3) shows dynamics of excess H$^+$ ion. Production rate of excess H$^+$ ions is assumed to proportional to the neoplastic cell density $N_2$ and also diffuse chemically. The first and second part in equation (3) show excess H$^+$ ion production with rate $r_3$ and reabsorption term with rate $d_3$, and the last part is diffusion with coefficient $D_3$. With this model, they can predict a pH gradient extending from tumor-host interface, and benign to malignant transition which consistent with experimental data.

Fig. 5. The linear process. Redrawn from figure 1b of Novak et al. (2003).

Next, as an example of stochastic model, the linear process is introduced (Novak, Michor and Iwasa, 2003). The linear process represents stem cells and differentiated cells with rule based cell division process. The model also has spatial structure, so-called compartment. It is very simple model. As shown in Fig. 5, N cells (9 in Fig. 5) are placed in a linear array and at each time step, one cell is chosen for reproduction proportional to its “fitness”. Then, the cell is replaced by two daughter cells and all cells beyond considering site are shifted one unit. The cell over the last edge falls off, it’s a representation of apoptosis. Repeating this rule and time goes on. The term fitness is one of the key concepts of this model and it is derived from reproductive rate of cell. One of the purposes of this model is to obtain fixation probability, it is a concept of evolutinal dynamics, i.e. the probability that one considering cell will take over the whole tissue. Despite the model has a spatial structure, the linear process could be categorized as a kind of population dynamics. It is apparent that sufficient vacant space adjacent to neoplastic cells is needed for its growth. Thus the invasion is very important in case of insufficient vacant space for neoplastic cells as in specific organ cancer. Malignancy of neoplastic cell arises by acquirement of invasion and
5. Conclusion and perspectives of the problem

From the early days of the discovery of radiation, its health effects have been recognized. Although numerous investigations have been done to clarify the health effects of radiation, there still seems to be many questions to answer. Existence of low dose radiation specific phenomena, e.g. bystander effects or adaptive responses (see Matsumoto et al, 2007 for review) shows possibility of unknown biological mechanisms, however there should be an intrinsic uncertainty within a system. One of the difficulties not only for radiation biology but also for general biology is thought to be presence of exceptions. It is possible that most experiments show “positive” results but a few experiments will show the opposite results in a biological experiments, and perhaps that is the big difference between biology and physics. Following the example of Mendel’s law, on the discovery of principle which is based on the biological mechanism will explain such kind of presence of exceptions with theoretically consistent. Here, one of the uncertainties of carcinogenesis is shown. Epidemiological data shows presence of the uncertainty about the age of cancer onset: ages of cancer onset are different among patients. By definition of “cancer onset” as an onset of neoplastic aggregate formation, detailed analysis of present model shows that cancer onset has initial condition dependency: very small differences in initial state will lead different ages of cancer onset. (unpublished data, NBO). This uncertainty seems to be stochastic, moreover, some specific minimum number “cancer onset number”, i.e. number of constituent cells of tumor, seems to be exist for the cancer onset (Fig. 22). However, a clarification of the cancer onset number problem needs further investigation.

Fig. 22. Temporal plots of cancer cell population at early stage of tumorigenesis. Each of the lines shows the calculation starting from different initial conditions. It seems to overcome a specific number of cancer cell for further tumor growth: red shaded region highlights the estimated hurdle in tumor growth.
Next, as another example of presence of exceptions, redundancy of the intracellular dynamics, e.g. metabolic network, is shown. It is thought that the redundancy is one of the factors of multi-pathway of carcinogenesis. Because of its redundancy, there seems to be many paths from some start point $A$ to the goal $G$ via intermediate point $B$, $C$, $D$..., thus even if some path $A$-$B$-$G$ is down, then another path $A$-$C$-$G$ will appear. This redundancy is the source of the stability of living systems. It is like a complicated subway route (Fig. 23).

We can reach our destination even if some station is down by accident using another route to the destination. It may indicate that more detailed analysis needs to be carried out in the near future. Moreover, on the investigation of tumorigenesis process, we should aware of the existence of adjacent cells.

Fig. 23. Simplified subway map of some big city. Due to the redundancy of network, we can reach our destination even if some station is down by accident. Similar structure may be seen in intracellular metabolic network.

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Since the discovery of X rays by Roentgen in 1895, the ionizing radiation has been extensively utilized in a variety of medical and industrial applications. However people have shortly recognized its harmful aspects through inadvertent uses. Subsequently people experienced nuclear power plant accidents in Chernobyl and Fukushima, which taught us that the risk of ionizing radiation is closely and seriously involved in the modern society. In this circumstance, it becomes increasingly important that more scientists, engineers and students get familiar with ionizing radiation research regardless of the research field they are working. Based on this idea, the book “Current Topics in Ionizing Radiation Research” was designed to overview the recent achievements in ionizing radiation research including biological effects, medical uses and principles of radiation measurement.

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