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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.

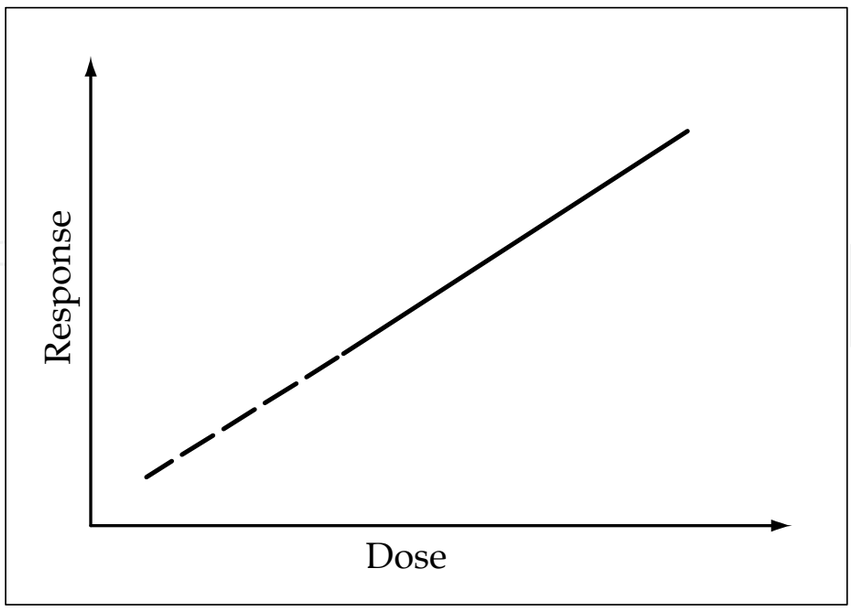


Fig. 1. Dose-response relationship of radiation effects. In general, cancer incidence is used for the response of radiation dose. Dashed line shows linear extrapolation from high-dose region.

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 diccovery 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 scientifical 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.

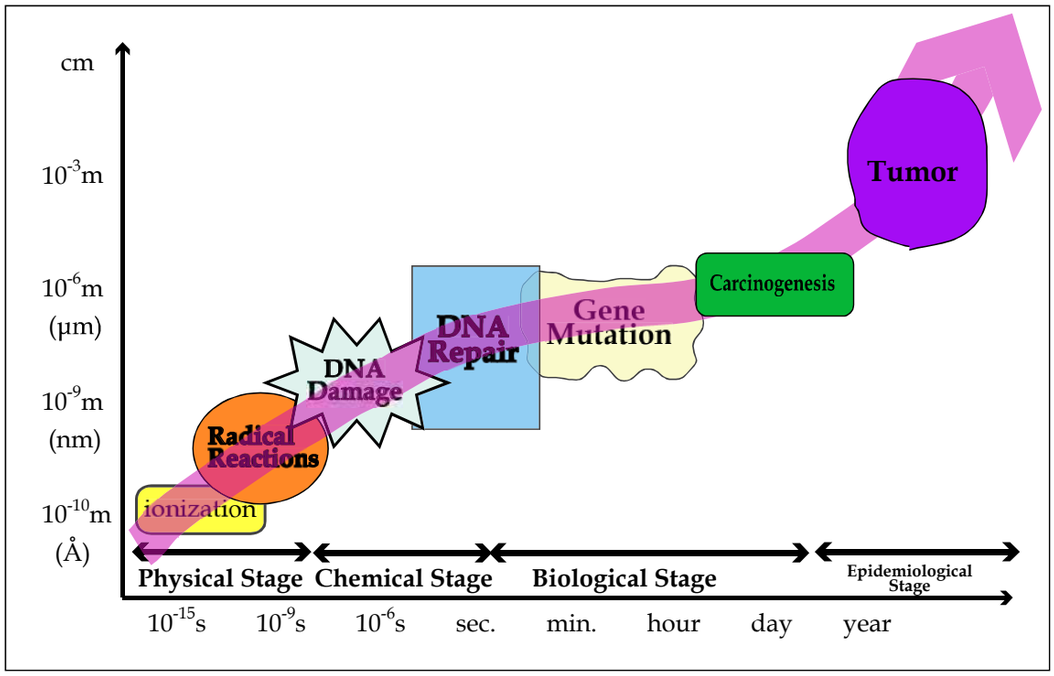


Fig. 2. Spatiotemporal order of radiation effects. Each event will progress to the tumor in a chain reaction as an arrow in the figure.

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 a 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 neoplasm may get the enhancement of cellular growth potential, i.e., they lost the intracellular communication. The last stage progression is thoght 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 a one of the aspects of the tumor growth process. Schematic explanation of tumorigenesis in association with IPP concept is shown in Fig. 3.

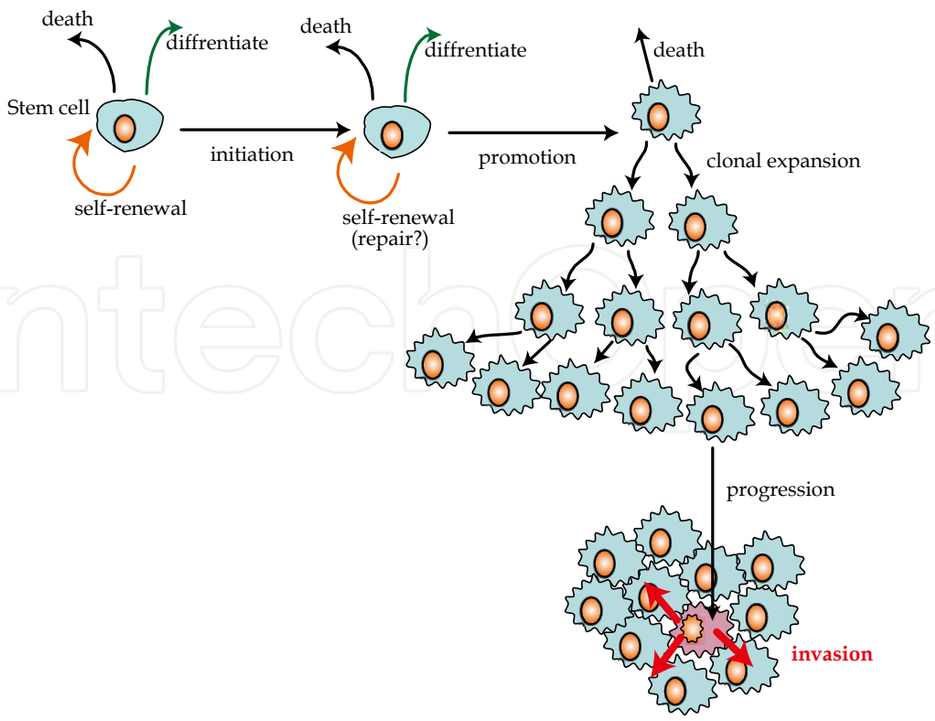


Fig. 3. Schematic explanation of tumorigenesis based on IPP concept.

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:

$$H_2O \rightarrow \bullet H_2O^+ + e^- , \quad (1)$$

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

$$\bullet H_2O^+ + H_2O \rightarrow H_3O^+ + \bullet OH , \quad (2)$$

or $\bullet H_2O^+$ breaks up:

$$\bullet H_2O^+ \rightarrow H^+ + \bullet OH. \quad (3)$$

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

$$e^- + nH_2O \rightarrow e_{aq}^- , \quad (4)$$

and e_{aq}^- will produce free radical •H according to:

$$e_{aq}^- + H_2O \rightarrow OH^- + \bullet H \quad (5)$$

or

$$e_{aq}^- + H^+ \rightarrow \bullet H. \quad (6)$$

Thus free radicals •OH, •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 unrepaired DNA damages or incorrectly repaired DNA damages, and these *prognoses* 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, misrepaired 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.

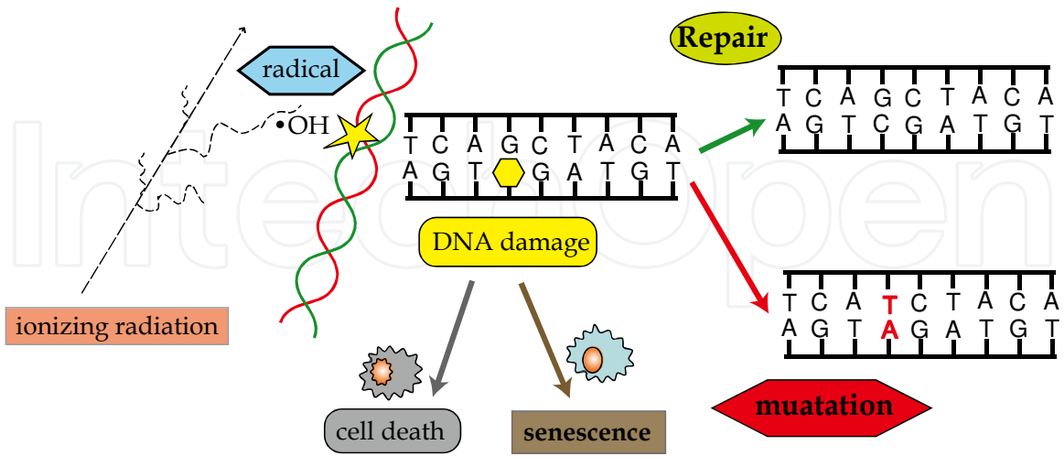


Fig. 4. Simplified schematic explanation of initial process of radiation effects, from DNA damage to mutation.

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.

$$\frac{\partial N_1}{\partial t} = r_1 N_1 \left(1 - \frac{N_1}{K_1} - \alpha_{12}\frac{N_2}{K_2}\right) - d_1 L N_1 + \nabla \cdot \left(D_{N_1}[N_2]\nabla N_1\right) \tag{7}$$

$$\frac{\partial N_2}{\partial t} = r_2 N_2 \left(1 - \frac{N_2}{K_2} - \alpha_{21}\frac{N_1}{K_1}\right) + \nabla \cdot \left(D_{N_2}[N_1]\nabla N_2\right) \tag{8}$$

$$\frac{\partial L}{\partial t} = r_3 N_2 - d_3 L + D_3 \nabla^2 L \tag{9}$$

The first part in Eq. (1) is growth term of normal tissue based on competitive Lotka-Volterra type equation with competition strength parameter α_{12}, where r_1 is growth rate of normal tissue, K_1 the carrying capacity, and the second term $d_1 L N_1$ is death rate of normal tissue

proportional to L, and the last part shows cellular diffusion with N_2 dependent diffusion coefficient $D_{N1}[N_2]$. Similarly, the first part in equation of neoplastic tissue growth (2) is growth term of neoplastic tissue with Lotka-Volterra competition parameter α_{21}, and second term is also cellular diffusion with N_1 dependent diffusion coefficient $D_{N2}[N_1]$ 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.

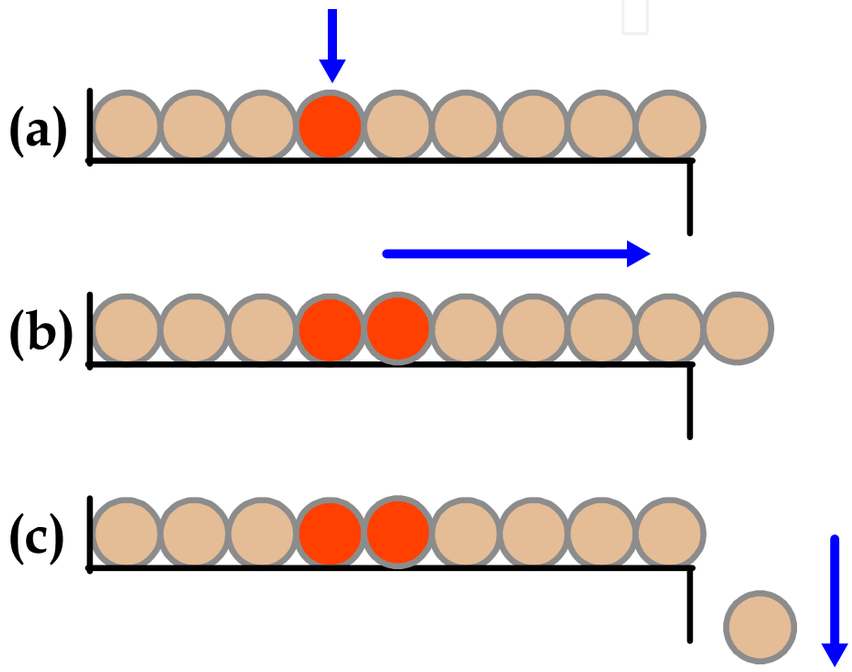


Fig. 5. The linear process. Redrawn from figure 1b of Novak et al. (2003).

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 evolutional 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

metastasis capability. On the modelling of tumorigenesis process, especially of solid cancer, existence of adjacent cells should be aware of. One of the important key dynamics of the invasion and metastasis is adhesion and microenvironmental adaptation. Moreover, in a stage of metastasis, we should consider a dynamics of respective cells rather than that of cell group's. Thus, it is thought that individual based cell model is applicable to model metastasis. The hybrid discrete continuum (HDC) model (Anderson and Quaranta, 2008) is one of such individual based cell models. The HDC model represents cells as points on a lattice which represents cell microenvironment, i.e. density of ECM and the concentrations of proteases and nutrients. The dynamics of cell microenvironment factors is defined by a set of continuous partial differential equations (PDEs).

Finally, multi-stage model proposed by Armitage and Doll (Armitage and Doll, 1954, Moolgavkar, 2004, Frank, 2007) is introduced. Armitage and Doll proposed multistage model in 1954 which was derived from excellent statistical findings about cancer mortality (Fisher and Holloman, 1953, Nordling, 1953). Fisher and Hollomon used statistics of stomach cancer in women from USA, and Nordling used statistics for all cancer in men from USA, United Kingdom, France, and Norway. Their data showed that the logarithm of cancer mortality increased in direct proportion to the logarithm the age between the ages of 25 and 74, the scale of the log-log plot showed sixth power of age; in other words, cancer mortality will increase with approximately the sixth power of age, $P=\alpha t^6$, where P is for cancer death rate, α the parameter, *t* is for age (Fig. 6).

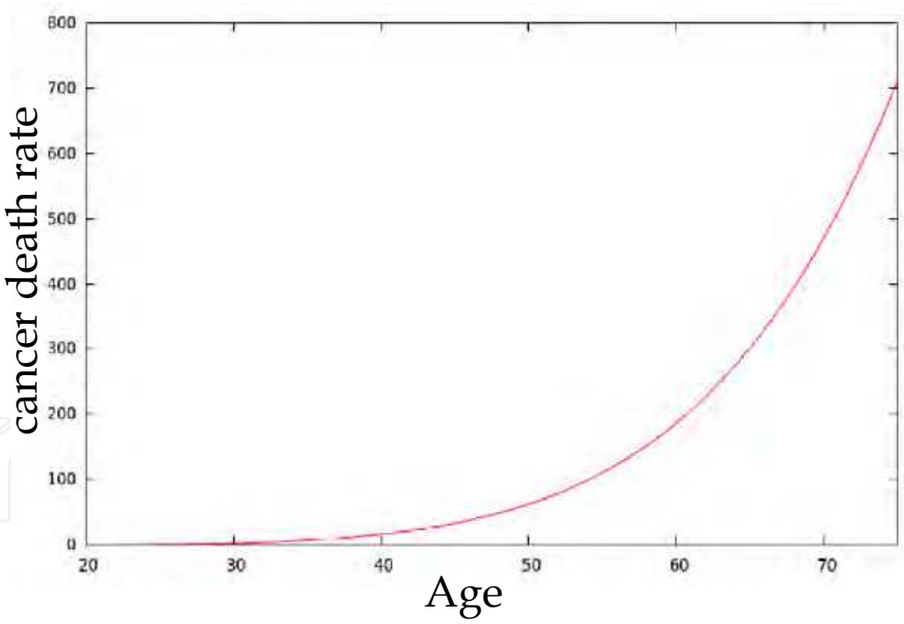


Fig. 6. Example plot of change in cancer mortality with age. Fisher and Hollomon, and Nordling used log-log scale for the plot of cancer mortality in their articles.

Thus, Armitage and Doll made a theory; human cancer is the end-result of several successive cellular changes and tested their theory by mathematical model (Fig. 7). Their model, so-called multistage model, has good agreement with many epidemiological data. Many followers of Armitage and Doll appear to refine multistage model to fit various specific epidemiological or biological data, thus there are many multistage variants (Frank, 2007).

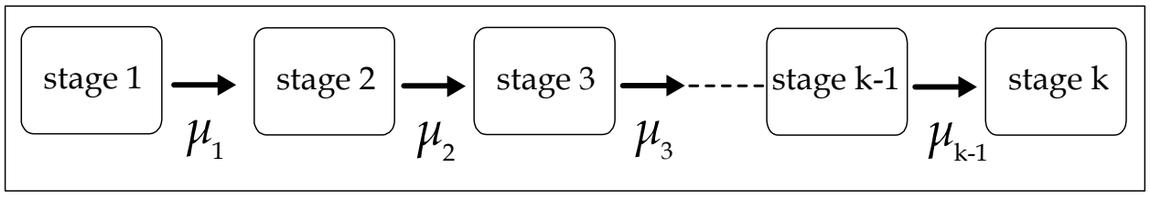


Fig. 7. Schematic explanation of Armitage-Doll multistage model. The cells acquire total (k-1) mutations with mutation rate μ_i where i=(1, k-1). The model supposes that an individual has a population of $N(t)$ normal cells at age t, then these cells acquire one mutation with a rate μ_1.Then cells with one mutation acquire a second mutation with rate μ_2, and so on. Cells with (k-1) are thought to be fully malignant cancer. Calculation of the population of malignant cells and its age are needed for statistical analysis.

The multistage theory could be summarized as follows,

$$P(t) = \frac{(Nu)^n t^{n-1}}{(n-1)!} \tag{10}$$

where P is cancer incidence, t is for age, n is the number of distinct carcinogenic events (number of stages -1), N is for number of cells at risk, u is for transformation rate per cell per unit time(Frank, 2007).

In spite of the multistage model was derived in 1954; it was about the same age as the discovery of DNA double helix, interestingly, it is thought to be a metaphor of biological fact: accumulation of carcinogenic mutations will induce cancer. Fig. 8 is a genetic multistage model of colorectal cancer (Fearon and Vogelstein, 1990). Today, carcinogenesis is known as the multistage genetic process with accumulation of mutagenic changes in the DNA. They derived mathematical structure from statistical data based on their mathematical knowledge. Their amazing modelling approach is instructive in constructing a model. However, the multistage model has some issues to be solved. For example, it seems to have no scientific evidence about the meaning of "stages" or number of mutations to fit the epidemiological data.

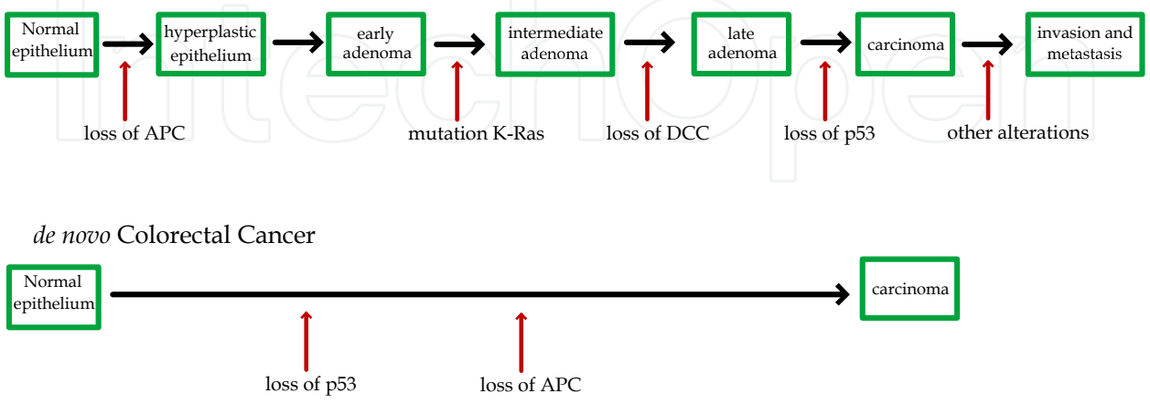


Fig. 8. Genetic multistage model of colorectal cancer. Most of colorectal cancer will follow upper pathway, however pathway like *de novo* type exists. Redrawn from figure 3 of Fearon and Vogelstein (1990).

4.2 Cellular large-*Q* Potts model

On the modelling of carcinogenesis process, it seems reasonable to introduce spatial structure to the model because of the fact that life and death of the cell is controled by its spatial strucuture, i.e., cell shape and cell size (Chen et al, 1997). These properties will not be ignored, because they will concern microenvironmental effects on the carcinogenesis process. Here we introduce one of the models of spatial cellular dynamics, called cellular large-*Q* Potts model (CPM) (Ouchi et al., 2003) which was first introduced by Graner and Glazier (Graner & Glazier, 1992, Glazier & Graner, 1993). The CPM is based on a biological hypothesis called differential adhesion hypothesis (DAH) first proposed by Steinberg (Steinberg, 1970). (Fig. 9). The problem "*How are tissues formed from populations of cells?*" is a one of the very famous questions in morphogenesis study (Gilbert, 2006, pp. 67). Steinberg showed certain cell types migrate centrally or peripherally depending on the accompanied cells, using cells derived from trypsinized embryonic tissues. From this observation, Steinberg made hypothesis that interacting cells will form an aggregate with the smallest interfacial energy because that is the thermodynamically stable. Therefore, cell adhesion strength of A-A is greater than A-B or B-B then sorting will occur. In the case of A-B strength is greater than or equal to strength of A-A or B-B then the aggregate will remain a randomly mixed structure. Finally, if the strength of A-B connection is so small compared to A-A or B-B connections, then A cells and B cells will make separate aggregates. It is considered that this mechanism is one of the principles of the dynamics of cell movement.

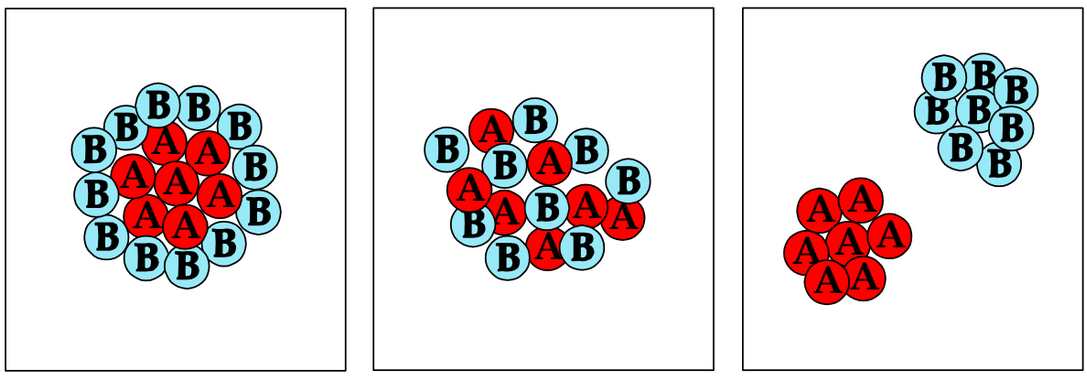


Fig. 9. Schematic representation of the DAH. Red circles with A, and Blue circles with B, represent two different types of cells. Mixture of these two types of cells finally makes spatial structure which is determined by their adhesive relationship. W_{xy} shows strength of cell adhesion between x and y.

4.2.1 Introduction of CPM

As a beginning we would like to introduce the CPM briefly. The CPM assigns a spin σ_{ij} to each lattice site, (i, j) and packed sites which have same spin number defines a cell, so the spin number is just a cell index which has no physical meanings. All movements of cells are determined by thermodynamic implementation of DAH, i.e. total energy of the system is

minimized by Monte Carlo method. Each cell has an associated cell type, τ. Fig. 10 shows schematic explanation of the formation rule of the cell of our model.

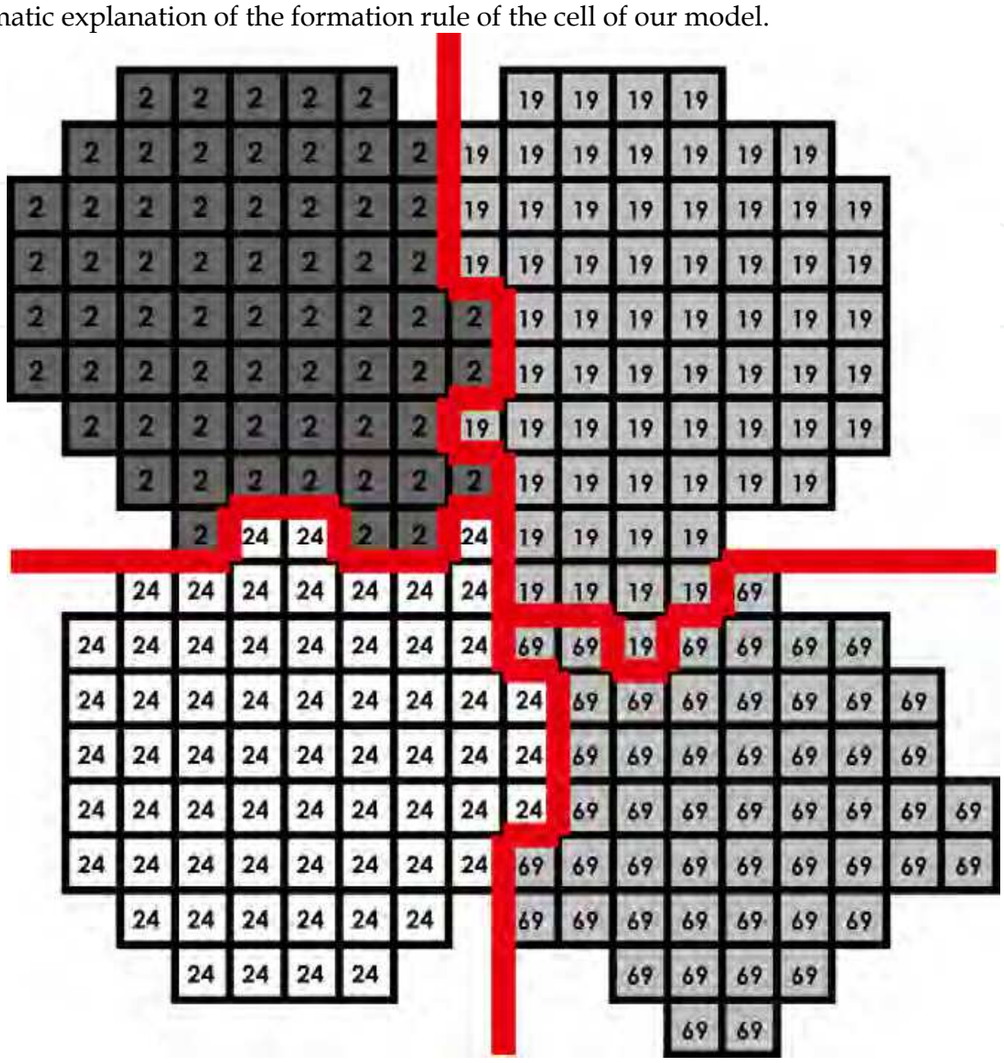


Fig. 10. Schematic explanation of the cell configuration of CPM. The numbers in a lattice shows σ_{ij} and each collection of σ_{ij} defines a cell. The colors of the each cell define the cell type, τ. A fat line in a figure shows the bonding sites of the cell. Redrawn from figure 2 of Ouchi (2007).

At the simulation, we calculate the total energy of the system H, from cell-cell or cell-substrate adhesion energy $J_{\tau,\tau}$ elastic bending energy of cell and surface tension energy. Thus, the total energy is

$$H = \sum_{(i,j)} J_{\tau\tau'}(1-\delta_{\sigma,\sigma'}) + \left\{\lambda_1 \sum_{\sigma}(a(\sigma)-A_\tau)^2 + \lambda_2 \sum_{\sigma}(l(\sigma)-l_\tau)^2\right\}(1-\delta_{\tau,m}) \tag{11}$$

where $a(\sigma)$ and $l(\sigma)$ are respectively the area and perimeter of considering cell σ, λ_1 and λ_2 are the elastic parameter of cell surface tension and bending. In this equation, the symbol δ_{ij} represents so-called delta function,

$$\delta_{ij} = \begin{cases} 1 & i = j \\ 0 & i \neq j, \end{cases} \tag{12}$$

it takes 1 if the index $i=j$, or 0 if the index $i \neq j$. In our 2D simulation, the cell size is introduced as a target area A_τ and a target perimeter l_τ. At each step, we apply the Metropolis algorithm, choose a site at random and accept a proposed change in its spin value with a Boltzmann transition probability dependent on temperature T >0:

$$P = \begin{cases} exp(-(\Delta H - H_0)/T & \Delta H > H_0 \\ 1 & \Delta H < H_0 \end{cases} \tag{13), (14}$$

where H_0 is a threshold for a spin flip adopted from Hogeweg (Hogeweg, 2000) and our temperature T is not a real world's temperature but just one of the controllable parameters. Fig. 11 is the detailed process of cell movement using this Metropolis algorithm. First we choose two adjacent sites located at cell surface randomly, and next changes one spin number to adjacent's spin number using above probability, and repeating again and again. Because of considering site with some spin number is a part of a cell with same spin number, spin number change represents cell deformation at cell surface. This is the cell movement.

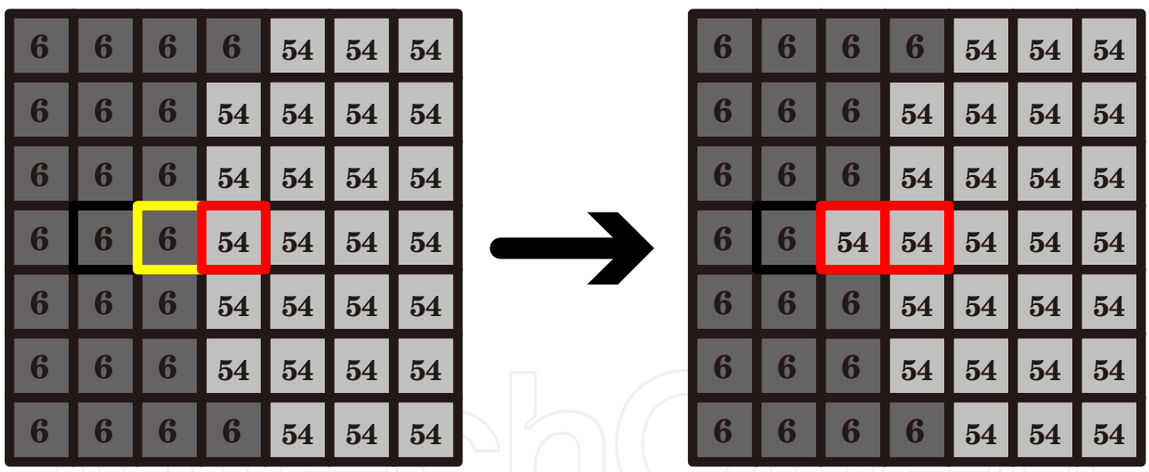


Fig. 11. Schematic explanation of the cell movement process of CPM. The site with spin number 6 is changed its number to 54. It shows that the cell 54 extend small part of its surface to adjacent cell 6.

Using this CPM formalism, we can simulate many types of cell group dynamics, e.g., the cell sorting, engulfment process and tissue rounding, moreover coupling with continuous field equations that depend on the solving problems, various cell group dynamics can be well simulated (Jiang, 2005, Turner & Sherratt, 2002) even for the entire life cycle of the slime mould Dictyostelium discoideum (Marée & Hogeweg, 2001). Fig. 12 and Fig. 13 are examples of the cell sorting and cell engulfment simulation. We used two cell types, endodermal cell and ectodermal cell, to simulate these cell rearrangement processes.

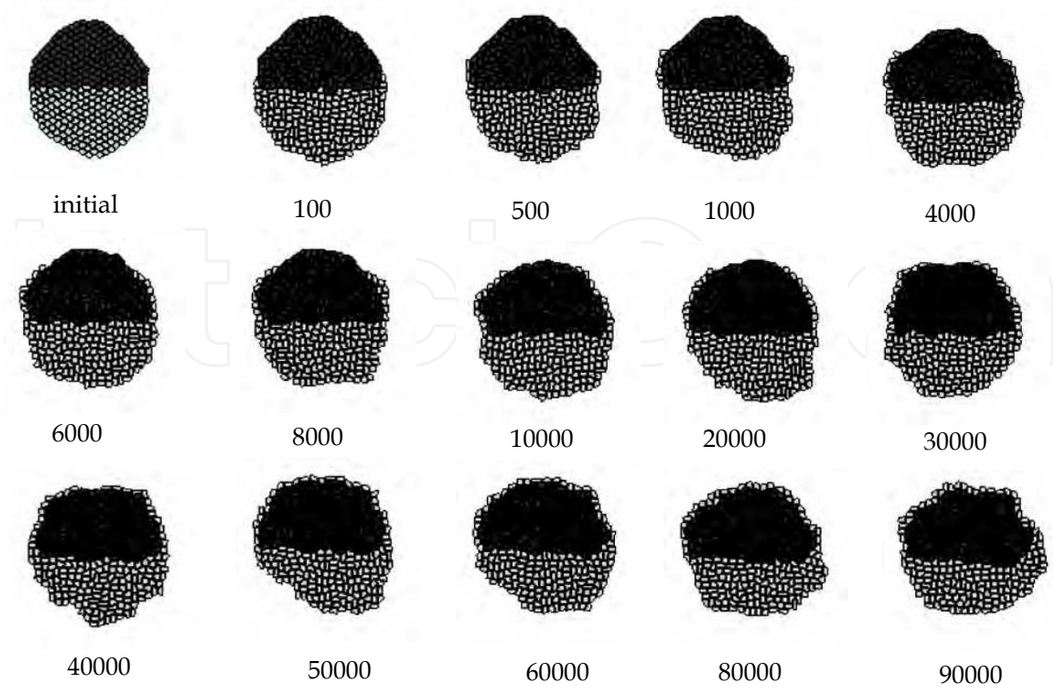


Fig. 12. Simulation of cell engulfment process using CPM. The numbers below each snapshot are simulation steps, Monte Carlo steps (MCS).

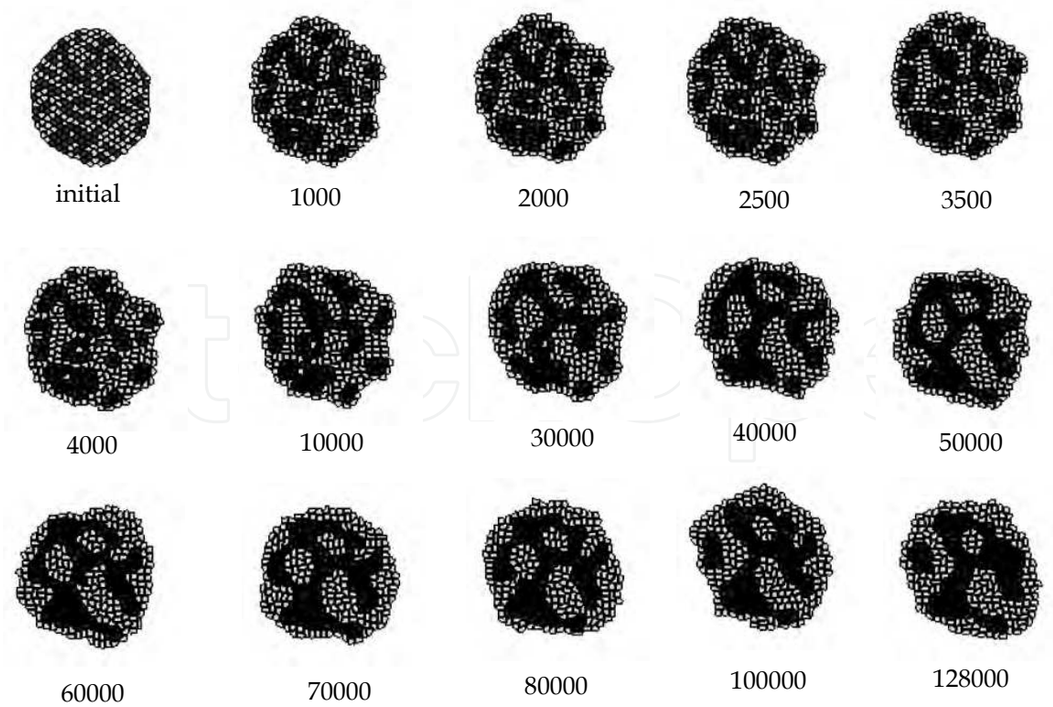


Fig. 13. Simulation of cell sorting process using CPM. The numbers below each snapshot are simulation steps, Monte Carlo steps (MCS).

The statistical calculations of mean square displacement (MSD) of cell, which is one of the characteristics of cell movement, agree with previous results obtained from corresponding experiments (Rieu et al., 2000). It seems that scientific validity of the CPM formalism is confirmed by these results.

4.2.2 Modelling of intracellular carcinogenesis process

Next, let us begin to model the cell transform process by introducing dynamics of cell type change in the CPM (Ouchi, 2007, Ouchi, 2011). Carcinogenesis process is commonly thought to be a multistage process, in which normal cells are transformed to cancer cells via accumulation of mutations. Modelling of cell transformation is achieved by employing cell type τ as one of the stages of multistage carcinogenesis. For the dynamics of cell transformation, three conceptual process, initiation, promotion and progression (IPP) of the cell are introduced in our model. Adding to these processes, cell killing and cell proliferation (cell division) are adopted to the model. All these dynamics are introduced as the probability of each process except for cell division. Cell division is introduced by conditional manner, i.e. if the cell size a exceeds the critical size a_c then cell division occur. Thus, adopted cell transformation dynamics (neoplastic process) can be drawn as Fig. 14, where P_1, P_2 and P_3 denote respectively the probabilities of initiation, promotion and progression, k_1, k_2, k_3 and k_4 are respectively the cell killing probabilities of corresponding cell types. According to the transformed cell types, this neoplastic process can be divided into four different cell stages, we call first cell stage as normal cell, second as initiated cell, third as promoted cell and final stage as cancer cell.

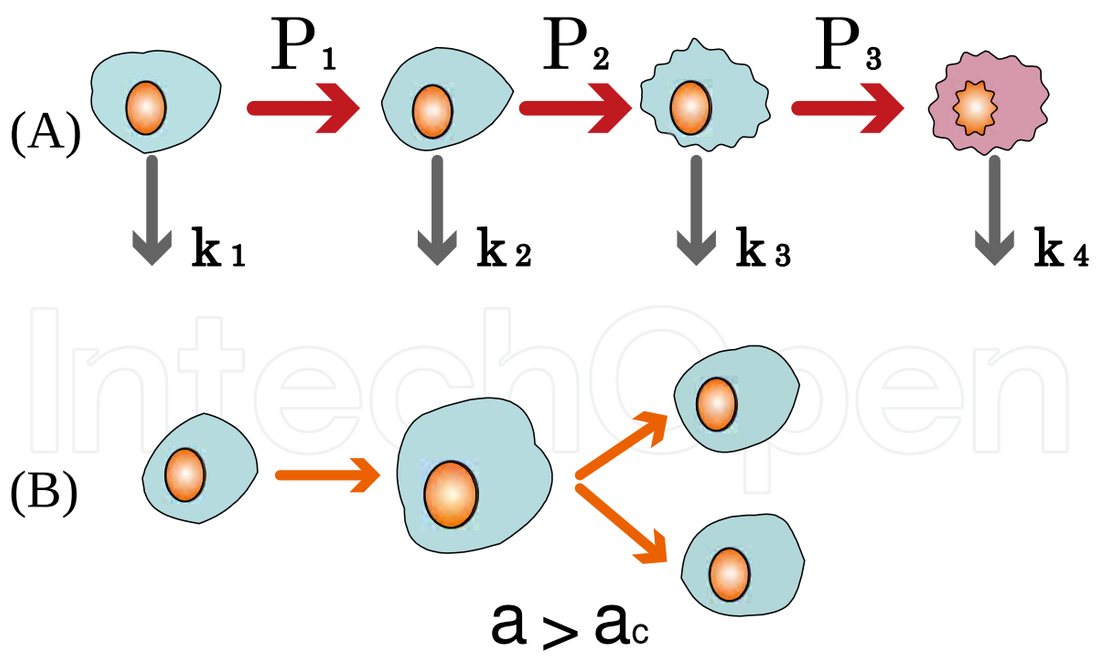


Fig. 14. Schematic explanation of cellular dynamics, intracellular (A) and cell division (B). In this figure, P_1, P_2 and P_3 are the mutation probabilities of each stage in the broadest sense, and k_1, k_2, k_3, and k_4 are the cell killing probabilities for each of the stages. If the cell area exceeds some threshold value, $a > a_c$, then cell division occurs (B).

By combination of intracellular dynamics and CPM which describes extracellular physical cell properties, mathematical model of tumorigenesis which has deformable sell shape and physical cell properties is introduced as shown in Fig. 15. The model has three specific physical properties, cell-cell or cell-medium adhision $J_{\tau\tau'}$, surface tension a, elastic bending l. The cells with diffrent cell type τ have different combination of physical properties ($J_{\tau\tau'}$, a, l), thus the cells will change its physical properties with the neoplastic transformation (Fig.15). As a concrete example, mutations in the genes involved in cell adhesion molecule change the physical adhesion of the cells. Therefore, adding to these physical parameters, the parameters of the model are the transformation probabilities P, the cell-kiling probabilities k, and the threshold cell size of cell division a_c. In this model, the effects of radiation will appear as the mutation increment or cell-killing increment. It is thoght that the radiation dose d and the mutation μ or cell kiling k have some relationship like $\mu=f(d)$ or $k=g(d)$, not a few experiments show linear relationship or linear quadratic rerationship depend on the situation. However, the clear relationship between dose and mutation frequency or cell-killing seem not to be obtained yet. Consequently, linear relationship between dose and mutation frequency or cell-killing is assumed: mutation increment means dose increment.
Generally, the physical parameters including the threshold cell size a_c could be determined with the aid of corresponding experiments, control parameters are thought to be the transformation probabilities P and the cell-kiling probabilities k. To show validity of the model described in this section, some simulation results are presented in the next section.

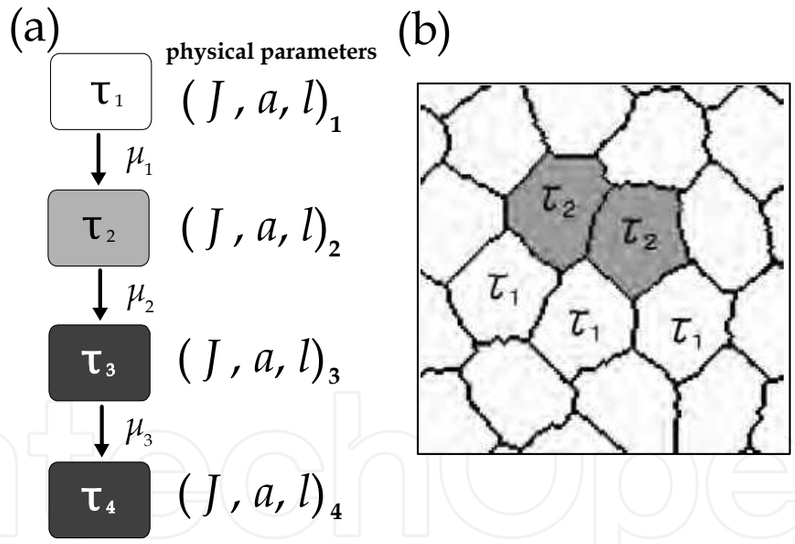


Fig. 15. Schematic explanation of the combination of intracellular dynamics and CPM. (a) The cells with diffrent cell type τ have different combination of physical parameters $(J, a, l)_i$, thus the cells will change its physical properties with the neoplastic transformation. The actual spatial configuration of the model is shown in (b).

4.2.3 Calculation results

Before starting statistical calculations, we carefully checked that the chosen parameters k_i and P_i satisfied homeostasis of the cell number; the total number of the cell is in equilibrium. In most cases, we use 250 or 1000 or 4000 cells to calculate statistical quantities depending on the situation. These available cell numbers are limited by the computational resources. In all

the calculation, we use randomly placed confluent normal cells mixed with small fraction (0.002%) of cells with initiation for initial condition of the system. Actually, changing this fraction has no influence on simulation results. In the simulation, as the transformation progresses, our cells are assumed to change softer and higher adhesion than the normal cells, for a first attempt of calculation. Figure 16 shows typical time evolution of the system starting from the initial condition, confluent normal cells mixed with a small number of cells with initiation. We can see the growth of the aggregate of cancer cells by using appropriate parameters (Ouchi, 2007, Ouchi, 2011).

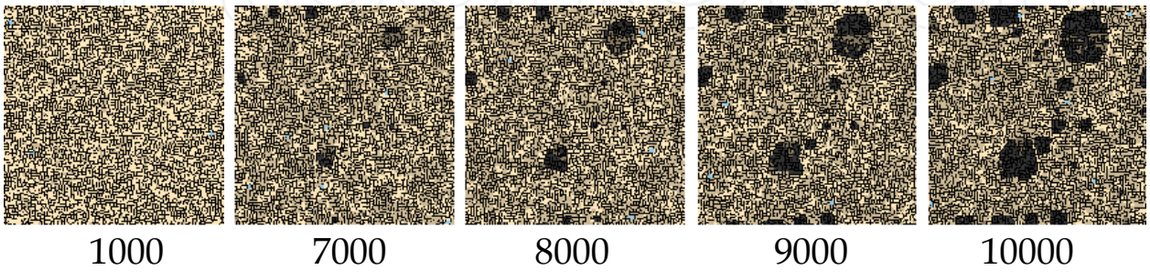


Fig. 16. Time evolution of the system. Time runs left to right. Numbers represent time steps. The initial condition is confluent normal cells mixed with a small number of cells with initiation. The system is consists of about 4000 cells. Darker cells represent higher stage of carcinogenesis, and black cells show cancer cells.

Next, population dynamics is shown in Fig. 17 (a) and Fig. 17 (b). The main diffrence between Fig. 17 (a) and Fig. 17 (b) is transformation parameters of the normal cell: P_1 and k_1 of (b) is five times gretaer than the (a)'s. In case of Fig.17 (a), no apparent tumorigenesis is seen, on the contrary, apparent tumorigenesis is seen in Fig.14 (b).

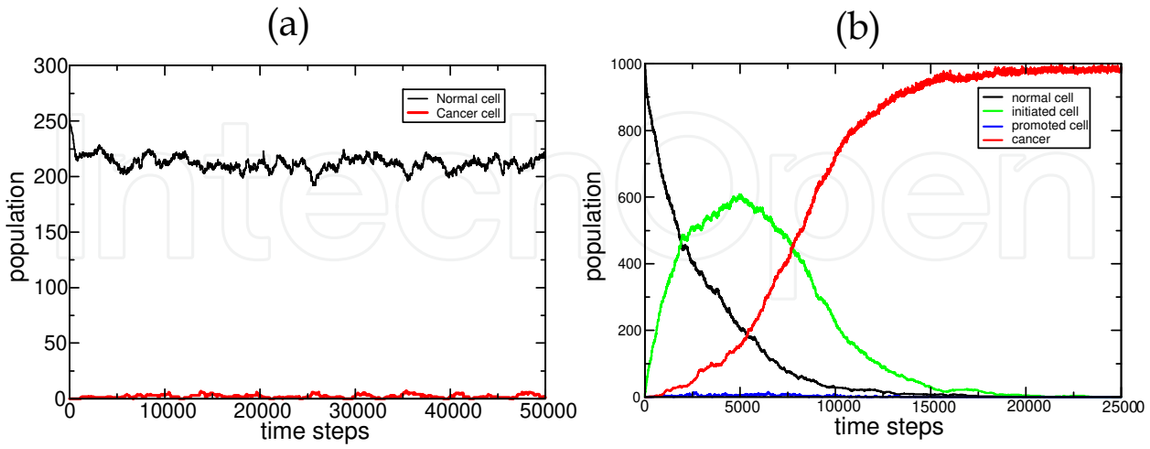


Fig. 17. Time series plots of the population for (a) normal cells (black line) and cancer cells (red line), and (b) normal cells (black line), initiated cells (green line), promoted cells (blue line) and cancer cells (red line). The saturation of the cancer cell number in (b) comes from the limitation of the system size.

Here, let us define a statistical quantity for criterion of tumourigenesis called "cancer growth rate" (*CGR*) : time averaged ratio of cancer cells to whole cells (Ouchi, 2011),

$$CGR = \langle \#\text{ of cancer cells}/\text{total }\#\text{ of cells}\rangle_t \quad (15)$$

where $\langle\rangle_t$ shows time averaging operation basically $t\rightarrow\infty$. Fig. 18 is plot of CGR calculation with changing initiation probability P_1 and fixed other parameters. Clearly two region can be seen, one is tumorigenesis region and the other is no tumor region, with some boundary value of $P_1\approx 0.003$.

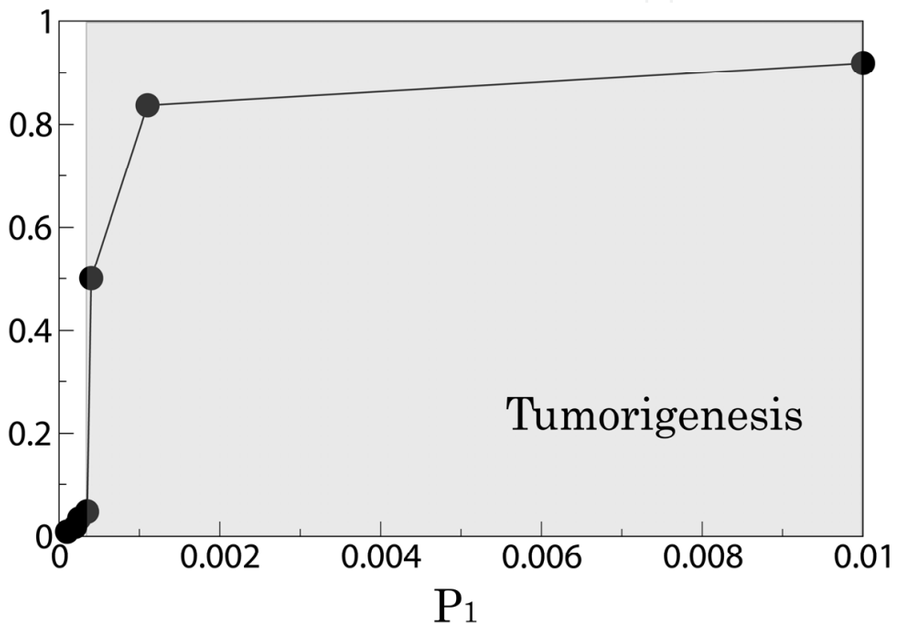


Fig. 18. Calculation of *CGR* with various P_1 values. It seems to have two regions, tumorigenesis and no tumor, depending on its P_1 value.

Finally, numerous calculations of *CGR* was performed to make phase diagram regarding the value of P_1 and k_1 of the model. Obtained phase diagram is shown in Fig. 19. If the calculated *CGR* is greater than 0.1, seems tumor to emerge, and thus *CGR*=0.1 is defined by the criteria of tumorigenesis. Tumor seems not to emerge if the *CGR* is less than 0.05. The tumorigenesis and non-tumorigenesis regions are separated by the linear function, $k_1=-\alpha P_1+\beta$, where $\alpha=3/2$ and $\beta=0.0006$.

Generally, tumor growth curve analysis is very important for the cancer study and also important for the risk assesement of low dose radiation. Usually, empirical models are used for growth curve analysis to fit obtained experimental data. In case of tumorigenesis, well-known Gompertz function (Gompertz, 1825) is used to analyze the data. Here, the present model is based on a modelling of biological mechanisms, a kind of bottom-up approach, calculation of growth curve of our model seems interesting subject: whether the growth curve of our model fit a empirical growth curve or not. In conclusion, it seems that the

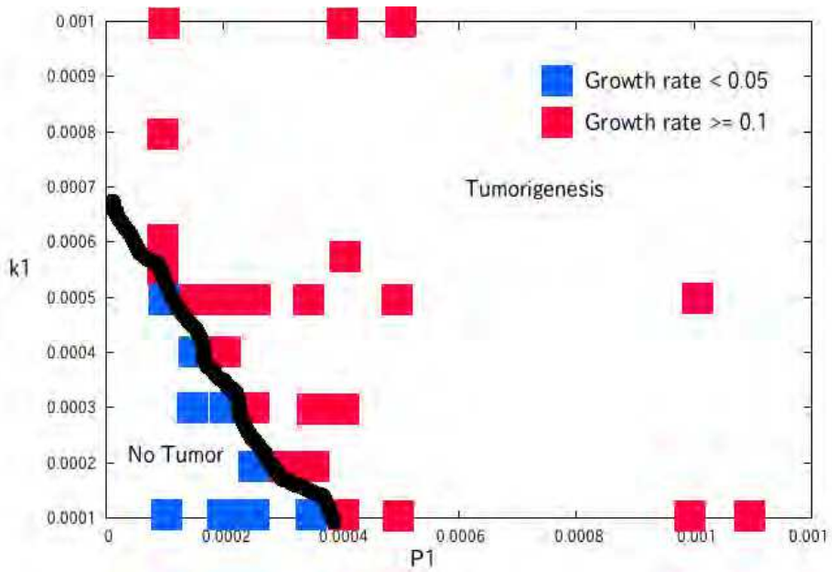


Fig. 19. Phase diagram of the model obtained by the CGR calculations in various combinations of P1 and k1, with other parameters are fixed. The (P_1, k_1) positions are painted by blue or red squares depending on its growth rates. The red squares show positions where the growth rate is greater than 0.1, and blue square positions are the positions where the growth rate is smaller than 0.05. The tumorigenesis and non-tumorigenesis regions are separated by the linear function, k_1=--αP_1+β, where α=3/2 and β=0.0006. Redrawn from figure 5 of Ouchi (2011).

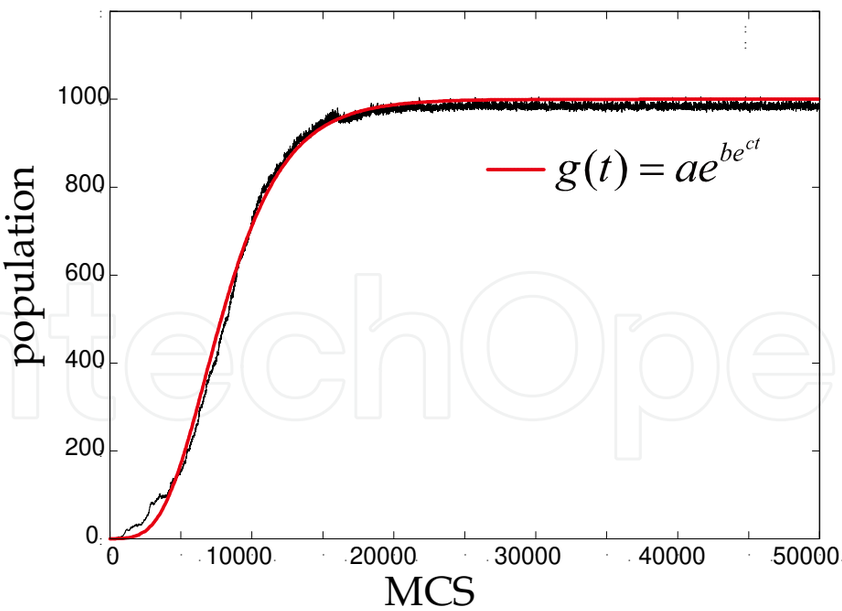


Fig. 20. Growth curve of cancer cells obtained from model calculation with parameters, P=(0.0005, 0.0001, 0.01), k=(0.0005, 0.001, 0.001, 0.001). Obtained growth curve seems to be fitted well with Gompertz function which is depicted in the figure by a red dotted line. The parameters of Gompertz function are a=1000, b=9.2, c=0.00033. Redrawn from figure 4 of Ouchi (2011).

model can reproduce the Gompertz curve very well as shown in Fig. 20. In a tumorigenesis region of our model, calculated tumor growth curves are well fitted with Gompertz curve with changing function's parameter (a,b,c). By changing model parameter ks and Ps, the different growth curve of Gompertz form are obtained, ordered structure of phase space is observed when we treat Gompertz function's parameters (a,b,c) as a point of 3D phase space (unpublished data, NBO). However, further investigation are needed to clarify the relation between phase space structure and cancer in real world.

4.3 Modelling tumor invasion and metastasis

Here, importance of invasion and metastasis study is explained. Tumor invasion and metastasis is one of the cardinal features of malignant cancer. It occurs after carcinogenesis, and is in the late stage of cancer. Tumor invasion and metastasis is a tumor spreading process from local to other organs (Liotta, 1984). The tumor invasion is the expanding process of cancer cells into neighboring normal tissue, and the metastasis is transporting process of the malignant tumor from its primary site to other distant sites in the body (Molecular Biology of the Cell, 5th Ed. [CELL], 2008). This metastasis may occur by three main routes: 1) through the bloodstream, 2) through the lymphatic system or through both routes, and in addition, 3) direct seeding across body cavities, e.g. through the peritoneum. Thus, the process of the tumor invasion and metastasis concern many cell types, e.g., normal cell, cancer stem cell, immune cell, extracellular matrix (ECM). In fact, these cells have complex interaction with each other to promote the cancer progression and expansion. Taking these behaviors into consideration, it is clear that cell-cell and cell-microenvironment interactions play a very important role in the process of invasion and metastasis. Tumor cells must be able to detach the primary site by changing its adhesion, and in turn must be able to attach the secondary sites, in order to proliferate successfully. Therefore, the adhesion is one of the key players for the invasion and metastasis. Moreover, cancer cells change its genetic status even in a metastatic period (Santinelli et al., 2008), thus the malignant cancer cells are thought to be not in a steady state but more dynamic. Therefore, tumor cells can grow up by "niche" adaptation in cell microenvironment, in other words, tumor need microenvironmental adaptation for its growth. The tumor cells which expand in the primary site become invasive and spreading to surrounding sites, and detachment of invasive tumor cells leading to the colonization of other organs. Tumor cells traveling to the distant organ should have microenvironmental adaptation to make colonies, consequently the tumor cells keep always evolving with changing its gene expression. This is a reason why the cancer is called as a microevolutionary process (Merlo et al., 2006). For that reason, tissue structure should be needed to model the dynamics of invasion and metastasis. In the present, there are not so many models introducing spatial tissue structure. It is not easy, but the tissue structure can be modeled by CPM formalism. In tissue modeling, we need more cell types, which depending on the considering tissue, to construct the system. Fig. 21 shows simulation example of the tissue structures, epithelium (a) and so-called intestinal crypt (b). It is believed that the cancer stem cells exist at the crypt, study of crypt structure is important for colorectal cancer. We use epithelial cells, medium layer, lamina muscularis mucosae, lamina propria for the simulation. By using one of these structures as an initial configuration of the stage of carcinogenesis, tumorigenesis and invasion could be studied integratively with presented model.

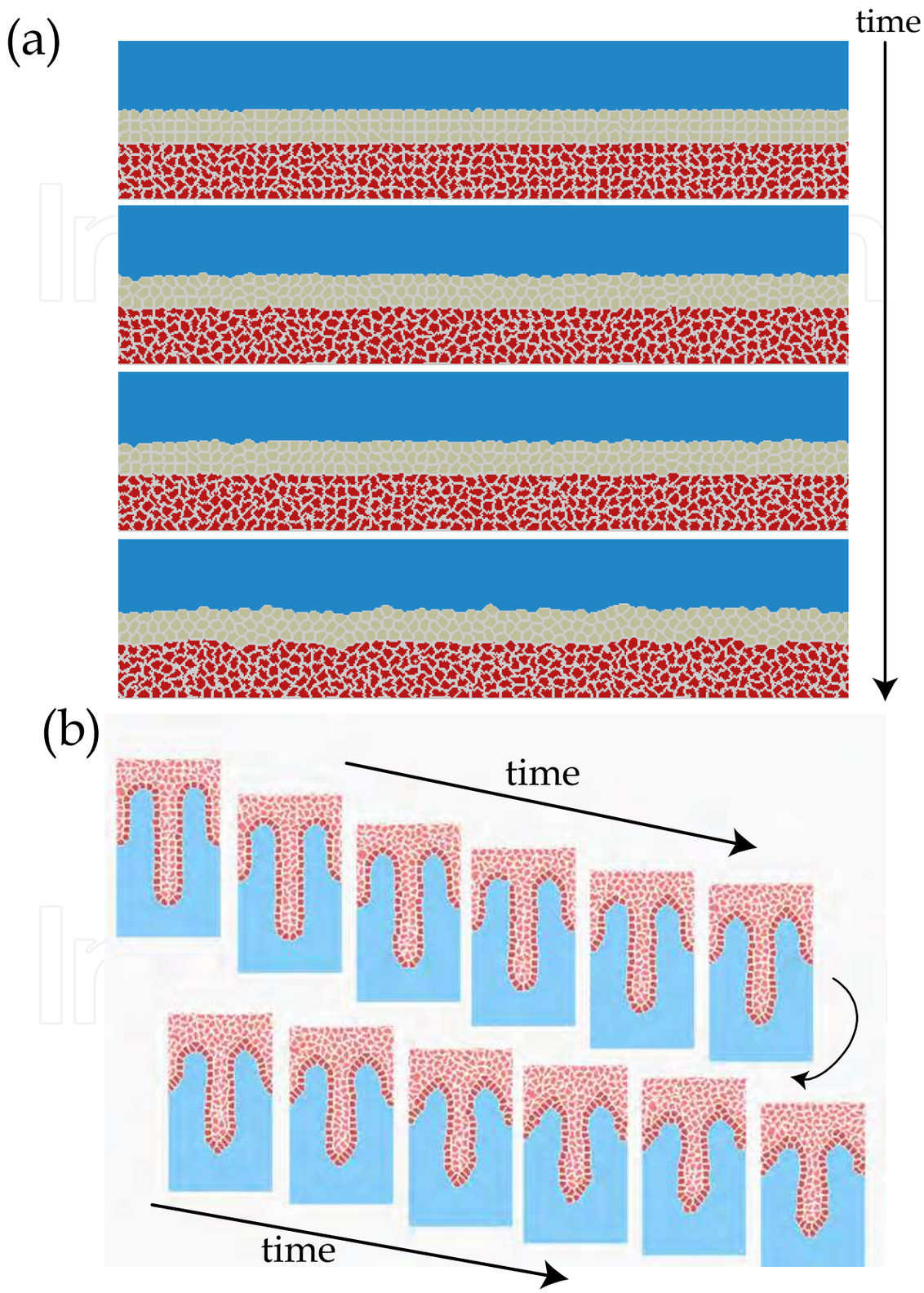


Fig. 21. Simulation examples of tissue structure using CPM.

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 a 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 diffrent 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.

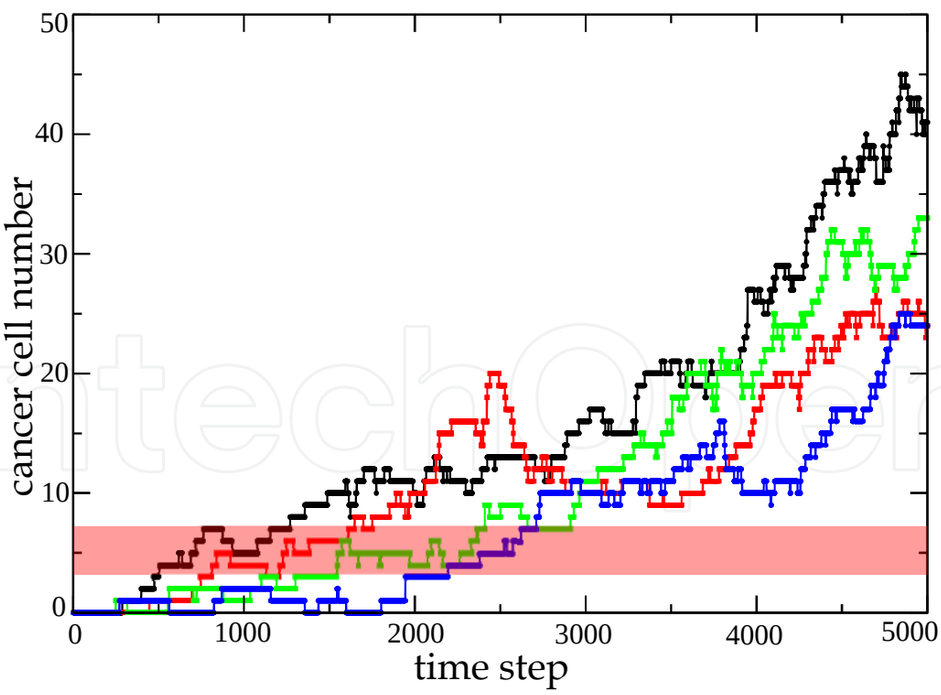


Fig. 22. Temporal plots of cancer cell population at early stage of tumorigenesis. Each of the lines shows the calculation starting from different initial conditions. It seems to overcome a specific number of cancer cell for further tumor growth: red shaded region highlights the estimated hurdle in tumor growth.

Next, as an 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.

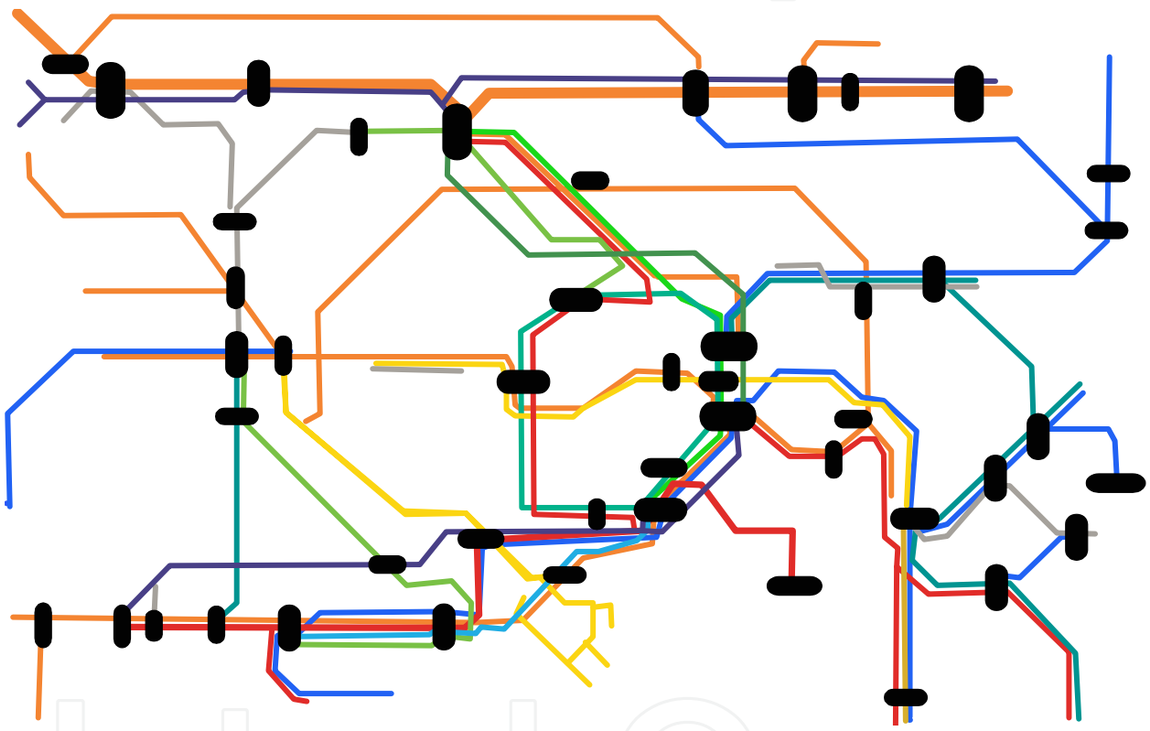


Fig. 23. Simplified subway map of some big city. Due to the redundancy of network, we can reach our destination even if some station is down by accident. Similar structure may be seen in intracellular metabolic network.

6. Acknowledgment

First, I would like to thank Dr. K. Saito for his continuous encouragement and useful discussions. Thanks are also due to Prof. M. Kai, Prof. M. Ootaki and Dr. O. Niwa for many suggestions and interesting discussions and holding very interesting and exciting small workshop about the mathematical model of carcinogenesis. Attending their workshop was author's best experience when he started this subject. The author also acknowledges all members of "SRB BENKYOKAI", it was very fascinating experience for me to attend the meeting and make interesting discussion. This work is partially supported by KAKENHI (18700294) and the Budget for Nuclear Research of the Ministry of Education, Culture,

Sports, Science and Technology, based on the screening and counseling by the Atomic Energy Commission.

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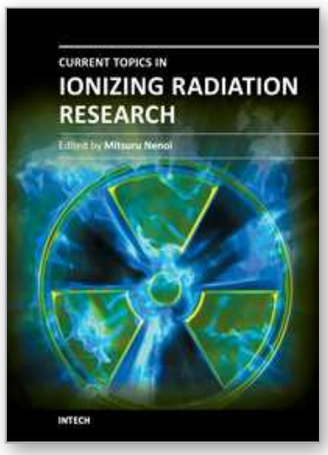
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Since the discovery of X rays by Roentgen in 1895, the ionizing radiation has been extensively utilized in a variety of medical and industrial applications. However people have shortly recognized its harmful aspects through inadvertent uses. Subsequently 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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