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On Mathematical Modelling for Immune Response to the Cancer Cells

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Abstract

We consider mathematical modelling for immune response to the cancer cells, and we propose a random model which describes cytotoxic effects to the cancer cells by effectors such as natural killer cells, cytotoxic T cells, and macrophages, etc. Then we shall analyze the model mathematically, and try to explain the qualitative properties of phenomena related to the host-defense mechanism.

Key Words : mathematical medicine, immune response, modelling and stochastic model

1. Introduction

1.1 Mathematical Medicine

The status quo of the mathematical medicine in Japan has kept on rejecting optimism. That is to say, the present situation keeps us, mathematical scientists away from collaboration of modelling and immunology with medical workers. That is partly because Japan has not brought up professional theorists who can deal with medical immunology, and partly because the experimenters being a minor group among the immunology researchers has little chances to be involved in the study of modelling. As a whole, in Japan we are facing at a critical phase that the academic region in Mathematical Sciences (including the modelling study) which is related to immunology remains an unexplored virgin field.

In order to resolve the pending problems and develop academic researches further, it is quite necessary for theorists and experimenters to meet each other halfway, cooperate with each other, and stimulate each interest in the researches. For instance, a mathematical medicine research group consisting of Prof. T. Suzuki and his coworkers is aiming at creation of a new research field as well as aiming at contribution towards practical scenes of medicine, by applying mathematics to the medicine positively and actively, cf. Collection of Abstracts in

Annual Meeting of Japan SIAM, 2010. Our stance in the study is, in its spirit, in the same line with theirs.

1.2 Purpose of Research

We consider the mathematical modelling of immune response to the cancer cells. Usually, normal cells N are transformed into irregular ones by some reasons, with the result that tumorigenic process of cells proceeds. On the other hand, a group of immune cells invokes the so-called immune response against the canceration, which is a central role in host-defense mechanisms. In this article we shall focus our mind on the immune response in the transformation period and in the disorder proliferation period of cancer cells, and we aim at construction of a random model which can describe the cytotoxic effect of effectors (such as natural killer cells, cytotoxic T cells, and macrophages, etc.) against the cancer cells X, and we would like to explain the qualitative properties of peculiar phenomena related to immune response, by analyzing the model mathematically.

We have investigated the formulation of catalytic processes applicable to filament description and catalyst action in Physiology and Biochemistry, the derivation of associated differential equations, the asymptotic behaviors, and the probabilistic representation of solutions to the partial differential equations which describe the particle movement in a random medium, for example, see Dôku (2000) Acta Appl. Math. Vol.63 and RIMS Kokyuroku (Kyoto University), Vol.1157, Dôku (2001) Sci. Math. Japn. Vol.54 and Quant. Infor. Vol.III, and Dôku (2001) RIMS Kokyuroku (Kyoto University), Vol.1193. In Dôku (2010) Far East J. Math. Sci. Vol.38, we studied the exsitence and uniqueness theorem as well as the long-time asymptotic behaviors for the model of measure-valued stochastic process with spatially dependent parameters. Such a stochastic model is very important because it can describe how the branching time of the corresponding random branching particle system becomes longer or shorter, and how the offspring increases or decreases in number according to the better or worse circumstance. In particular, we investigated a special class of singular superprocesses in a series of papers: Dôku (2003) Far East J. Theo. Stat. Vol.9, Dôku (2006) Adv. Appl. Stat. Vol.6 and Sci. Math. Japn, and Dôku (2008) RIMS Kôkyûroku Bessatsu, B6. Those models are extremely important because they can realize the chemical reaction of drugs. Moreover, we considered limit theorems of measure-valued Markov processes which are closely related to population genetics.

We divide our purpose into two categories: one is the short-term purpose, and the other is the long-term purpose. As for the short-term purpose, we raise the following three:

> (i) To construct a mathematical model which is able to describe the cytotoxic actions of effectors against cancer cells (here we propose such a stochastic model);
> (ii) To analyze the model mathematically;
> (iii) To study the qualitative properties of the biological phenomena related to immune response.

As for the long-term purpose, in the near future we are going to explain the following:

(iv) To explain an extraordinary phenomenon (such as the saturation of immune effectiveness), from the viewpoint of model theory.

Furthermore, we have already announced our main results of this article at the organized session: "mathematical medicine" in the annual meeting of Japan SIAM, held in Meiji University, Tokyo on September 8, 2010, and have also talked about them at the session of disease I in the twentieth conference of Japan Society of Mathematical Biology, held in Hokkaido University, Sapporo on September 14, 2010, see Dôku (2010) Collection of Abstracts in Annual Meeting of Japan SIAM and Dôku (2010) Collection of Abstracts of the 20th JSMB. We are also going to give a talk about the results in the seventh conference on the theory of biomathematics and its applications, which is to be held at the Research Institute for Mathematical Sciences, Kyoto in November, 2010.

2. Mathematical Modelling

We divide our modelling process into several phases, and we shall consider and explain it step by step in what follows.

2.1 Proliferation Process of Cancer

The aim of this section consists in modelling the proliferation process of cancer cells. Since our goal is, roughly speaking, to construct a mathematical model for host-defense mechanisms against cancer, the so-called immune response is a very important keyword. Actually, what we have in mind about the immune response is as follows. We shall give it in a very simple way. First, normal cells are transformed into irregular ones by some reasons. Here any specific reason does not matter, namely, we do not care any individual reason. Then the tumorigenic process of cells proceeds, and finally a group of immune cells invokes immune response (cf. Figure 1). It is well-known as host-defense mechanisms against cancer. The figure 1 illustrates the situation where the macrophage which has been activated by the interferon (IFN-α) and interleukin (IL-8) with the help of T helper cell (Th cell), is attacking the cancer cell. As to the subject, in this article we focus our mind especially on the immune response in both cases: both in the transformation period and in the proliferation period of cancer cells. Next we consider the effectors being countermeasure of cancer, which should be carefully chosen. What we have in mind about effectors is as follows: for examples, natural killer (NK) cells, cytotoxic T cells, and macrophages, etc. (see Figure 2). The figure 2 illustrates the effectors such as (a) macrophage, (b) NK cell, and (c) cytotoxic T cell. These effectors are main characters in our model, and especially we consider the activated macrophage, which plays an important role in the immune response as far as mathematical modelling is concerned. As we have reviewed above, some reasons cause transformation of cells, then those cells cancerate. More precisely, malfunction of oncogene or tumor suppressor gene evokes continual proliferation signals, and finally cancer cells repeat disorder proliferation (cf. Figures 3 and 4). Figure 3 illustrates the situation, where normal cells are transformed into irregular cells (= cancer cells), and they start off disorder proliferation. Figure 4 also illustrates a similar situation. On the other hand, a group of immune cells or effectors (such as NK cells, cytotoxic T cells

and macrophages, etc.) prey on and destroy cancer cells. As a matter of fact, by virtue of the immunological surveillance the effector is coming about the scene of irregular proliferation in the affected area, and sticks to one of cancer cells and makes a bound body together with the unfortunately chosen cancer cell, and kills it by the cytotoxic effect.

Taking the above into consideration, we propose the following proliferation model. Let N_n be the total number of cancer cells in the n-th generation. Actually, for each $n \in \mathbb{N}$,

$$N_n : \Omega \to \mathbb{N}$$

is an $\mathbb{N}$-valued random variable. We assume that there exists a sequence of positive numbers $\{\gamma_n\}_n$, $\gamma_n > 0$ satisfying

$$\gamma_n \to \gamma \in \mathbb{R}^+ \qquad (\text{as} \quad n \to \infty)$$

for some positive number γ. Let Z_n denote the number of offspring to be produced. Its expectation is given by

$$\mathbb{E}[Z_n] = 1 + \frac{\gamma_N}{n}$$

and its variance satisfies the condition

$$Var(Z_n) = \sigma_n^2 \to \sigma^2 \ (< \infty) \qquad (\text{as} \quad n \to \infty).$$

So, we assume that the branching mechanism is asymptotically supercritical, and we consider the situation where there exists the second moment of Z_n even in the limit as n tends towards infinity. As to the proliferation or cleavage, each cell divides independently at random time. Here we realize it by giving the branching rate $n\lambda$ with $\lambda > 0$. This means that we assume the accelerated proliferation. In other words, it implies that, if the branching rate is λ simply, under the condition that the parent cell is alive until time t, the probability that the cell dies in the small interval $[t, t + \delta t)$ is given by

$$\lambda \delta t + o(\delta t).$$

2.2 Spatial Movement of Cancer

As to domain, it is restricted to the immune response in a local tissue, so it is sufficient to consider a bounded domain

$$D \subset \mathbb{R}^d \qquad (d = 3).$$

Since we consider the spatial movement of cancer, we need to describe its starting point. So that, for each $n \in \mathbb{N}$ given, let $x_i^{(n)} \in \mathbb{R}^d$ be the initial location of the i-th cell among N_n cancer cells in the n-th generation, for $i = 1, 2, \ldots, N_n$. Here our target cell is of course a cancer cell. It is observed that there is almost little movement in the initial period, namely, in the transformation period, and they have oozing liquid-like diffusion in the disorder proliferation period. Hence we suppose that they obey a diffusive movement with a diffusion coefficient including a small parameter ε (> 0).

Moreover, we also consider the spatial movement of cancer caused by its extraordinary proliferation. Because of its concentration with high density, we need an interaction effect, in

a sense, in the diffusion of cancer. Indeed, this is realized by specific functions. Let $h \in C^1$ be a function describing the strength of interaction, and ρ denotes a parameter indicating the interaction effect. More precisely, on a mathematical basis, we assume that the function h itself and its first derivative h' belong to the same L^2 space, i.e.,

$$h(x),\ h'(x) \in L^2.$$

Then the function ρ is defined by the integration of h, that is,

$$\rho(x) = \int h(x-y)h(y)dy.$$

Define $k_0 = c^2 + \rho(0)$ as a positive constant, and $k(\varepsilon) = \varepsilon k_0$. We set

$$L_\varepsilon = k(\varepsilon)\Delta \qquad \text{with} \quad \Delta:\ \text{Laplacian}$$

2.3 Cytotoxicity of Effectors

Next we consider the cytotoxicity of effector against cancer cells. We realize it as a positive constant

$$q > 0 : \text{the strength of cytotoxicity of effector}$$

It just corresponds to the emigration rate in the terminology, which is stemmed from the theory of branching processes.

3. A Random Model by Superprocess as the Limiting Process

Under the circumstances stated above, we consider the random model for cancer. As a matter of fact, we propose an empirical measure $X_t^{(n)}$ as our stochastic model, which is given by

$$X_t^{(n)} = \frac{1}{n}\sum_{i=1}^{N_n(t)} \delta_{x_i^{(n)}(t)}. \tag{1}$$

It is nothing but a measure-valued stochastic process, where $N_n(t)$ denotes the total number of cancer cells alive at time t, and $x_i^{(n)}(t)$ is the location of the i-th cancer cell among the n-th generation at time t, for $i = 1, 2, \ldots, N_n(t)$. Actually, our proposed model can be regarded as the following quantity. Counting up all the designated cancer cells alive until time t, and summing all of them flagging one among all the members in the n-th generation, and moreover the quantity is multiplied by some scaling factor or a certain weight that is given by here $1/n$. It is interesting to note that the weight term may possibly possess an alternative expression realized by other scaling. In other words, we can say that our proposed model $X_t^{(n)}$ is the process describing the random cloud of cancer. Some stochastic process X_t can be obtained as a limit of $X_t^{(n)}$ as n tends towards infinity. Such a limiting process is called the superprocess. It is expected that this superprocess X_t reflects the qualitative properties of the proposed random model. So in what follows, we will analyze the superprocess X_t only, instead of $X_t^{(n)}$.

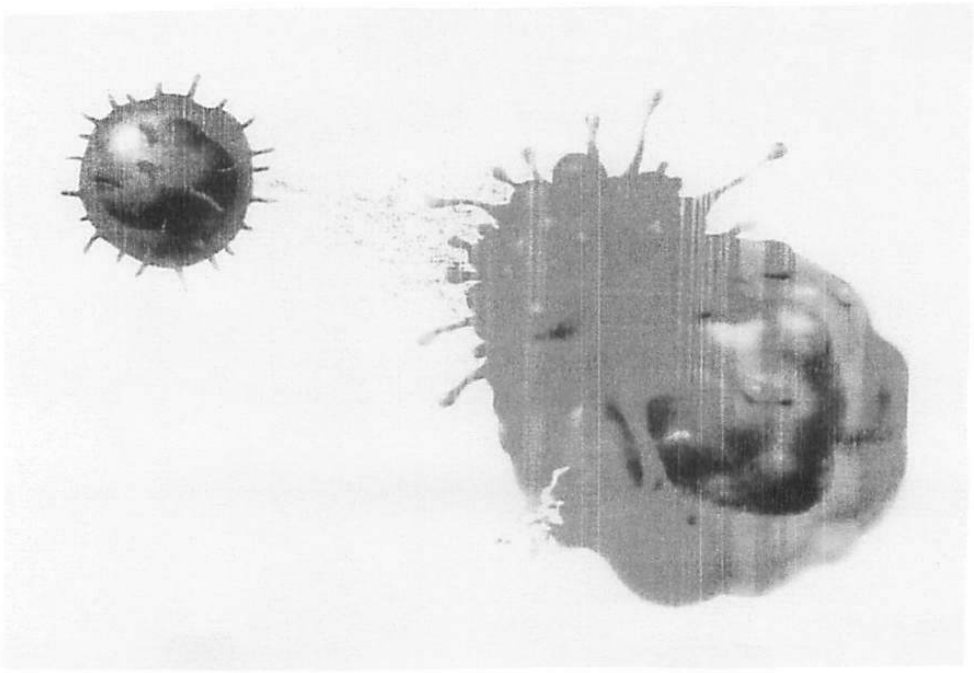
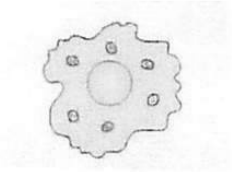
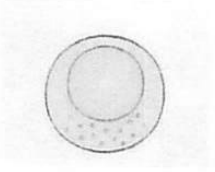


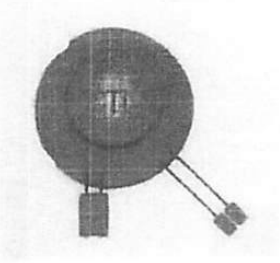
Figure 1. Cytotoxic effect of macrophage



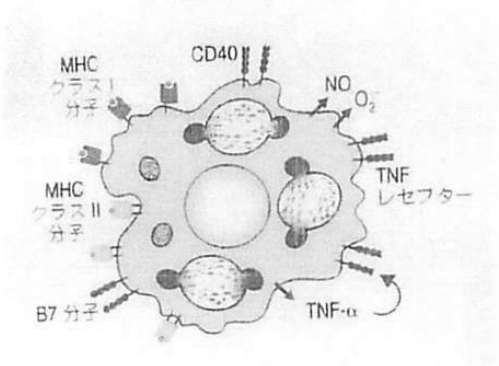
(a) a macrophage



(b) a natural killer cell



(c) a cytotoxic T cell



(d) an activated macrophage

Figure 2. Effectors: A group of immune cells

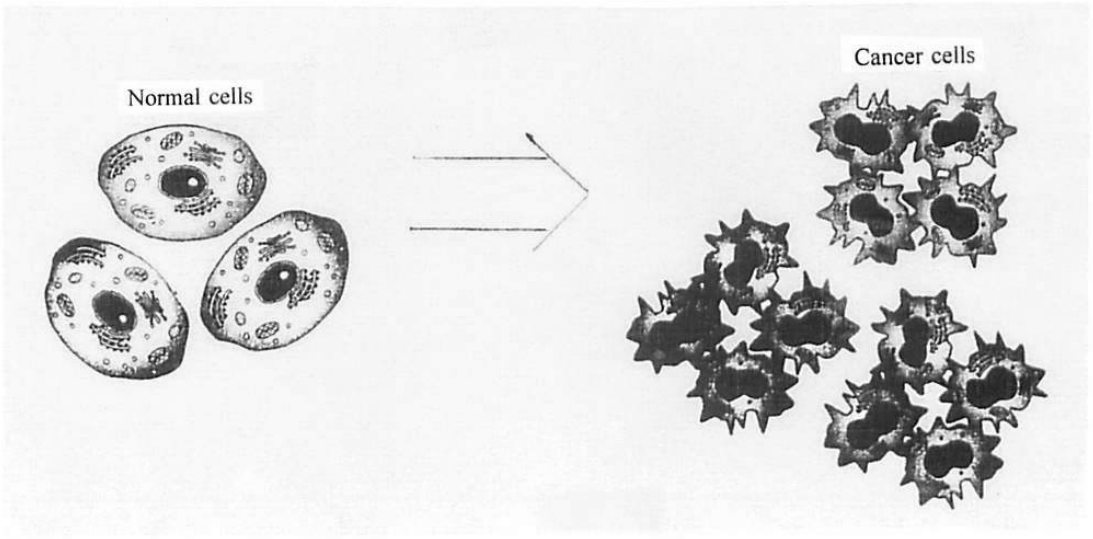


Figure 3. Tumorigenic process proceeds

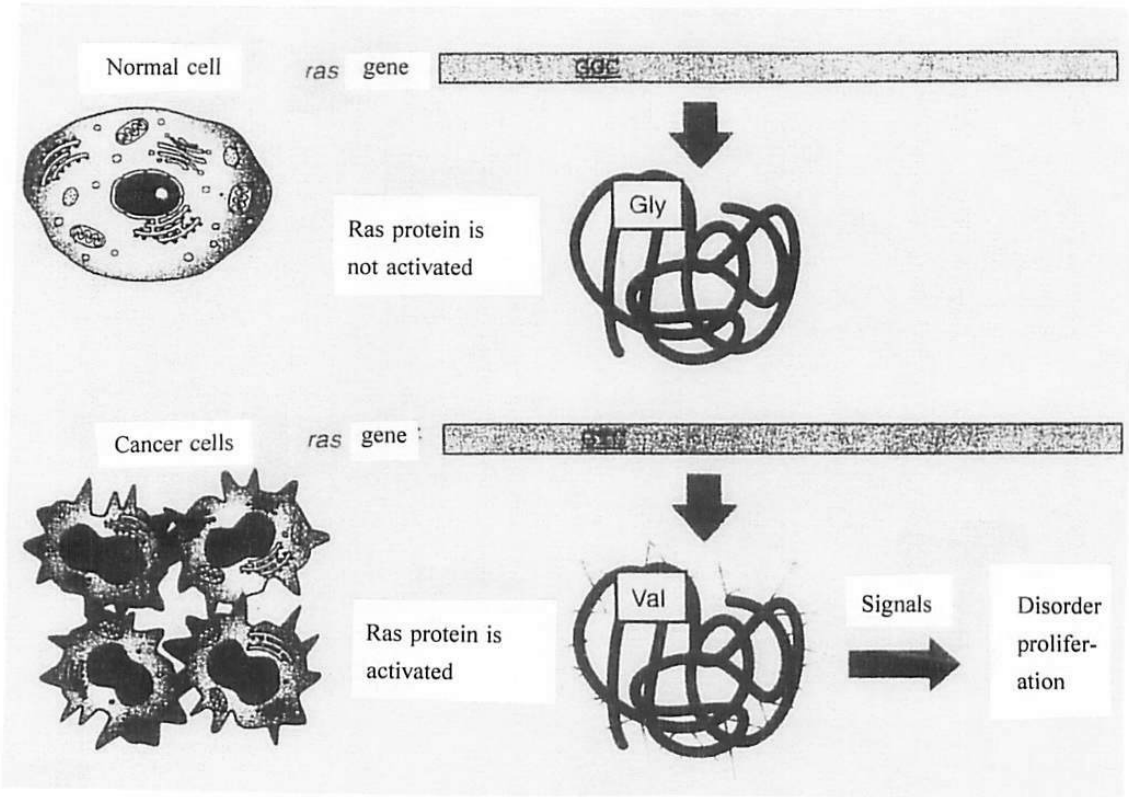


Figure 4. Canceration

4. Principal Results

4.1 Existence Result

First we are going to introduce the existence result.

Theorem 1. *If the initial data*

$$X_0^{(n)} \equiv X_n(0) = \frac{1}{n}\sum_{i=1}^{N_n} \delta_{x_i^{(n)}} \tag{2}$$

converges weakly to a finite measure $\mu \in M_F$, then the proposed empirical model $\{X_n(\cdot)\}_n$ converges weakly to a finite measure-valued process $X = \{X(\cdot)\}$.

The above theorem guarantees the existence of the model, which we are going to analyze mathematically.

4.2 Results on Uniqueness and Regularity

Next we shall introduce a regularity result as well as the uniqueness result. We begin with defining some useful operators.

$$\mathcal{A}F(\mu) = \int_{R^d} L_\varepsilon \frac{\delta F(\mu)}{\delta \mu(x)} \mu(dx) + \frac{1}{2}\iint_{R^d \times R^d} \sum_{i \neq j} \rho_{ij} \partial_{ij}^2 \frac{\delta^2 F(\mu)}{\delta \mu(x) \delta \mu(y)} d\mu d\mu \tag{3}$$

for a proper test function F defined on the space of finite measures M_F. Here the symbol $\delta F(\mu)/\delta \mu(x)$ denotes the variational derivative of the test function F with respect to a measure μ at x in the functional analysis. This $\mathcal{A}$ is an operator that controls spatial movement of the superprocess.

$$\mathcal{B}F(\mu) = \frac{1}{2}\int_{R^d} \tilde{\sigma} \frac{\delta^2 F(\mu)}{\delta \mu(x)^2} \mu(dx). \tag{4}$$

This $\mathcal{B}$ is an operator that controls the branching mechanism of the superprocess.

$$\mathcal{C}F(\mu) = -\int_{R^d} q \frac{\delta F(\mu)}{\delta \mu(x)} m(dx), \tag{5}$$

where m is a reference measure on R^d. This operator $\mathcal{C}$ describes the influence of cytotoxicity to cancer cells by the effectors. Furthermore, we define

$$\mathcal{L} = \mathcal{A} + \mathcal{B} + \mathcal{C}.$$

Theorem 2. *For every $\mu \in M_F$ with compact support, the limiting process $X = \{X_t\}$ solves the martingale problem $(\mathcal{L}, \delta_\mu)$-MP.*

Theorem 3. *The process $X = \{X_t\}$ is a M_F-valued Markov process.*

4.3 Characterization of the Limiting Process

Actually, the above-mentioned theorem 2 not only guarantees the uniqueness of the superprocess, but also provides with a characterization of the superprocess X_t. Indeed, the following assertion is valid as well. That is to say, there exists a unique probability measure $\mathbb{P}_\mu$ defined on the space of M_F-valued continuous paths $C([0,\infty);\, M_F)$

$$\exists_1\, \mathbb{P}_\mu \in \mathcal{P}(C([0,\infty);\, M_F))$$

satisfying
(a) $\quad X_0 = \mu, \quad$ a.s.
(b) For each $F \in \mathrm{Dom}(\mathcal{L})$,

$$F(X_t) - F(X_0) - \int_0^t \mathcal{L}F(X_s)ds \tag{6}$$

is a continuous $\{\mathcal{F}_t\}$-martingale. Here the measure $\mathbb{P}_\mu$ is nothing but the probability distribution of the superprocess X_t.

5. Expected Results

There are some remarkable results which we can expect from our stochastic model. First, longtime asymptotic behaviors of X_t is, of course, obtained. Especially when the constant is the typical case $c = 0$, with a minor hypothesis, it is possible that the singular process may appear under a suitable scaling. This indicates that our proposed model has a potential capability of describing the catastrophic situation.

Next we shall introduce an important result named "local extinction" of the process X_t. Before stating it, we need to make a quick review on the concept of local extinction. What is the transience? What does it mean that the process X_t is transient? In fact, we say that the support $supp(X)$ is transient if for any open set B,

$$\mathbb{P}_\mu(\, X_t(B) > 0,\ \exists\, t \geq 0 \mid X(\cdot) \text{ survives}\,) < 1$$

holds. That is, under the assumption that the process $X(\cdot)$ survives, the probability of the event that the process X_t has a charge on the set B for some time $t \geq 0$ is less than one, which means that the probability that the process is absent on B for some time t is positive, i.e., such an event may possibly take place. On the other hand, what is the local extinction? We say that the support $supp(X)$ exposes a local extinction if for each bounded set B, there exists a finite random time ζ_B such that

$$X_t(B) = 0, \quad \forall t \geq \zeta_B$$

holds. Namely, the process X_t has no charge on the subset B for any time t after some time, whcih means that the cancer cells are absent in the region B after a suitable time, that is possible. Notice that local extinction is a much stronger condition than transience. In fact, we can expect that the superprocess X_t exposes a local extinction. In other words, it is equivalent to the fact that the effectors succeed in expelling the cancer cells localy out the territoty, that is, this model has the ability to realize the admissible phenomenon that effectors are locally predominant over cancer. That is why this property is extremely important.

6. Concluding Remarks

In this last section we will refer to the final target in our study. We consider the following two things related to effectors in immune response side:

- Killing capability against cancer
- Multiplicative capability of effector

From the viewpoint of comparison of the above two capabilities, it is said that there exists a upper bound called "the saturation of immune effectiveness", for which SIE stands. The final purpose is to explain the existence of such SIE theoretically, by using our stochastic model.

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