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Tumor-immune system analysis code situation, relationship with real states and its automatic control

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Abstract Tumor-immune system interaction can be expressed by eigen-value problem. Then if the state of eigen-value = 1 exist actually, the effect of the state is thought to be big for the deletion of tumor. So here, the mathematical existence of the state was shown by simulation. Moreover, the state of eigen-value = 1 seemes to be necessary when the proliferation rate of a tumor is high. This is discussed. To know how tumor-immune system works automatically is important, moreover the state of eigen-value = 1 has an automatic control function to a certain extent. So what are necessary additionally is discussed.

1. Introduction

In the therapy of cancer, it seems that the thought of dynamical system includingeigen-value problem shown in [1], where quantitativeness is kept about important information, may not be considered for the purposes to have perspective and quantitative prediction by this mechanism in medical areas.

In other words, it means that the space where the thought to use dynamical system to know important aspects of each cancer disease and to use them for its treatment is left.

When we think about the application of dynamical system and eigen-value problem to tumor-immune system interaction analysis, there are mass actions which can be analyzed quantitatively as eigen-value problem, and there is the state where eigen-value = 1 called local ignition here. This state can be an abrupt and strong effect to cancer cell deletion and may not be considered in the actual medical area. This is quite different from the activation of T cell which produces IL2 and Teff. This means that a possibility to have a big effect to the treatment by the application of this state is left. If the state of eigen-value = 1 actually occurs, the quantitative analysis of this state with eigen-value is relevant.

Here IL2 ・・・・・ interleukin 2
Teff ・・・・・ effector T cell

In section 7 it is shown by simulation that the state of eigen-value > 1 and that of eigen-value <1 can exist.

[About Local ignition]Especially if there can be the state in an actual situation where eigenvalue = 1 which I call "local ignition" here because it can be considered a kind of continuous firing caused by the mass of T cells and IL2 with "local" which means the firing has a limited area covering a solid mass expressed by its eigen vector in many cases, the effect must be so big that it must cause a very strong attack to cancer theoretically. This is quite different from the activation of T cell which produces IL2 and Teff.

So it seems that to show a quantitative analytical clear structure and a useful information valuable for treatments is important.

Mass action caused by mainly by T cells IL2 must exists theoretically. This is a phenomenom expressed by mathematics quantitatively

This is expressed as eigen-value problem although the eigen-value and the eigen vector slowly vary through the phenomenom.

It is imagine that when eigen-value = 1, a very strong attack against a tumor or a pathogen will occur. So if this can occur actually, it is both very useful and dangerous because it may damage many healthy cells.

So If the state of eigen-value = 1 can occur in the real body, followings can be considered.

(1) By knowing the behaviors quantitatively through analysis, it is imagined that this analysis and information may be used for treatments.

(2)It is said widely that when an immune system response is too strong, healthy cells may be damaged,the immune system response should be restrained to a necessary level. If eigen-value increases over 1 at all, the levels of [T] and [IL2] increase without limits theoretically.

Here [T] ••••• the density of T cells

[IL2] ••••• the density of IL2

So in such a case immune system must restrain to a necessary but a low level. This leads to the automatic control of immune system.

Near the state of eigen-value = 1, the immune system behaves as if it tends to have an automatic control to be appropriate for the purpose to a certain extent. But some additional conditions seems necessary.

So here it includes open questions

(This is discussed in section 3.)

(3) When the proliferation speed of a cancer is higher than a some level, a strong attack by immune system seems to be necessary. Then the reach to the state of eigen-value = 1 is necessary.

(This is shown in section 5)

Here, eigen-value problems are used for various areas very effectively, especially it is used in a nuclear technology where there a similarity between tumor-immune system interaction and the nuclear technology in their behavior. Generally speaking, dynamical system is said to be qualitative, but eigen-value problem has quantitative aspects through eigen value, etc..

When we think about how we can contribute to the treatments using dynamical system, to stimulate and cause a strong positive feedback is, if possible actually, seems very valuable.

2. Why a simulation is necessary ?

Generally speaking, concrete cases where dynamic behaviors with space-time variables and two or three dimensional space are considered and they are expressed by partial differential equations can not be expressed but by simulation.

Monte Carlo simulation is one of the methods to express. It does not depend on equations, it has merits one of which is that a special environment like its structure in the simulation space can be taken into account more easily.

Generally speaking, the concentration speed of Monte Carlo simulation is said to be very slow in comparison with other methods like digitized methods like finite difference methods. So in past days, Monte Carlo method was not used often. But now each personal computer has a huge computation power like a super computer in past days. So Monte Carlo simulation can have a enough possibility for them to be used in actual situations.

To conduct a simulation by a diffusion equation, because many aspects of tumor- immune interaction behaviors are thought to be diffusion, and for the result to be compared with the result by Monte Carlo simulation must be better.

3. About a conjecture of the automatic control mechanism of immune system, especially thought by T cell activity through the state of local ignition with eigen-value = 1

Immune system must have an automatic control mechanism which fits to be appropriate for its purpose that is to protect our bodies although there are autoimmune diseases. And to know the mechanism may become valuable.

In the situation with eigen-value = 1, the immune system behaves like with an automatic control system appropriate for its purpose to a certain extent.

(1)When eigen-value = 1, if the number of cancer cells increases a little, the eigen-value becomes a little larger than 1 however small the upper part from 1 may be, and the number of Tact and the density of IL2 around solid cancer continue to increase without limit theoreticallyuntil the increased number of the cancer cells goes back to the original number by increased number of Teff.

Here Tact ••••• activated T cell

This behavior seems appropriate for the purpose to a certain extent.

[Additional necessity]

But unnecessarily big increase of number of Tact and accompanied Teff increase are said to be damaging because it is apt to cause autoimmune as said widely.

So it is necessary for the state with eigen-value >1 to be taken back to the state with eigen-value =1 swiftly when [Tact], [Teff] and [IL2] are enough big or appropriately big. Then the appropriate levels of [Tact], [Teff] and [IL2] are kept constant as far as eigen-value =1.

Here [Tact] ••••• density of Tact

(2)On the other hand, with eigen-value = 1, if the number of cancer cells decreases a little, the eigen-value becomes a little smaller than 1, however small the lower part from 1 may be, then the number of Tact decreases.

So in this case it is imagined that the number of cancer cells will increase again until the decreased

number of the cancer cells increases to the original number.

[Additional necessity]

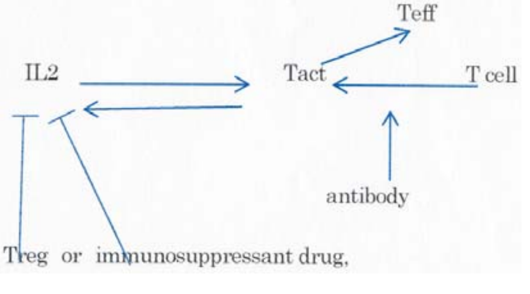
So here even if the number of cancer cells decreases a little, the eigen-value must be kept 1 to keep thelevels of [Tact] , [Teff] and [IL2] are kept constant and appropriate.

As shown above, these levels are kept constant as far as eigen-value =1.

Here [Teff] ••••• the density of Teff

4 About how the state of immune system especially by T cells and IL2 becomes positive feedback and how it becomes eigen-value problem.

For the situation to become positive feedback and eigen-value problem, IL2 is thought to work predominantly.



Here Teff ••••• effector T cell

Treg ••••• regulatory T cell

- Immunosuppressant drugs shown in [2] restrain IL2 production from T cells.From here there is a possibility to be able to know the quantitative relationship between [IL2] and the degree of immunosuppression.

When eigen-value = 1, it is imagines that an abrupt immunosuppression is caused by a little decrease of [IL2] as the steepslope at eigen-value = 1in Fig.1 shows.

It is known that Treg also suppresses immune system through suppressing IL2 secretion from Tact.

Through these facts, if a necessary set of data is available, there is a possibility in a future where the effects of Treg and immunosuppressant drugs can be simulated.

5 When the proliferation speed of tumor cells is high, the state of eigen-value = 1 and local ignition seems to be necessary.

When we know the examples where cancer is cured completely, there it is imagined from its strong activity and its attack of immune system that local ignition may be caused.

(1) When the proliferation speed is very slow, a little T cell activity which can be called subignition here (eigen-value < 1) can cause the deletion of all cancer cells theoretically.

(2) When the proliferation speed becomes higher than some level, the state of eigen-value =1 seems to be necessary because the level of [Tact] increases without limit theoretically as shown in.Fig. 1.

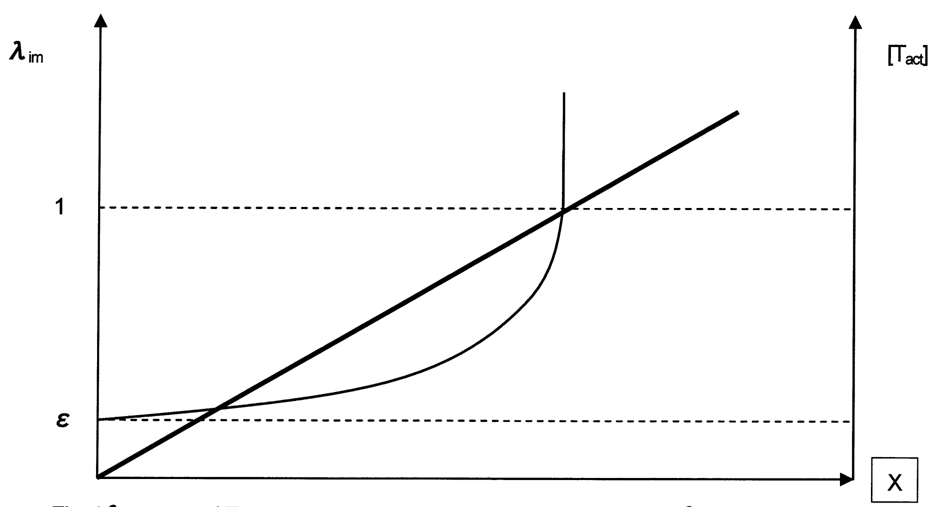


Fig. 1 λ_{im}v.s.x and T_{act}v.s. x graphs. Here x is total effect to increase λ_{im} like [IL2]

——— •••λ_{im}

——— ••[T_{act}]

x ••• Total effect to increase λ_{im} like [IL2]

ε ••• Entering Th cells and Tc cells with a high affinity into the field model constantly to a cancer peptide

6. Computation examples by the computer code being developed

Here computation examples by a computer code being developed are shown.

The purpose of the examples is to show there are two cases one of which means the occurrence of the state of eigen-value > 1 and the local ignition, the other of which means the occurrence of the state of eigen-value < 1 and the subignition. From this standpoint and the lack of actual data, the data set used in these simulation is tentative one not actual one. So the results mean only the confirmation of the existence of the above two cases.

6.1 The main points of the computer simulation

(1) The simulation code uses Monte Carlo simulation method.

(2) Amoeboid movements of T cells are expressed by the choice of a moving direction at each time computed from uniform random numbers and a moving distance computed by a given mean free path and the uniform random numbers

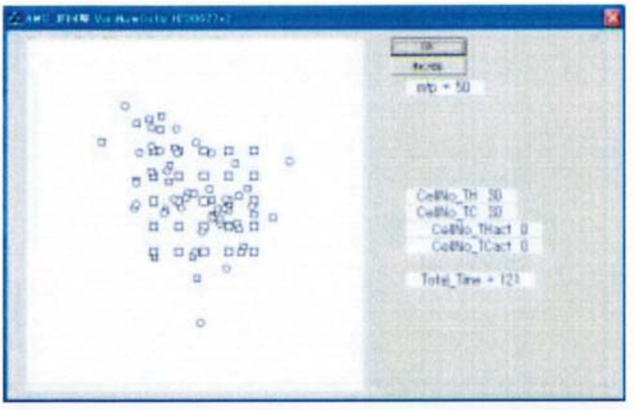
(3)The level of [IL2] is increased according to the level of [Tact]. The level of [IL2] determines the proliferation speed of T cells.

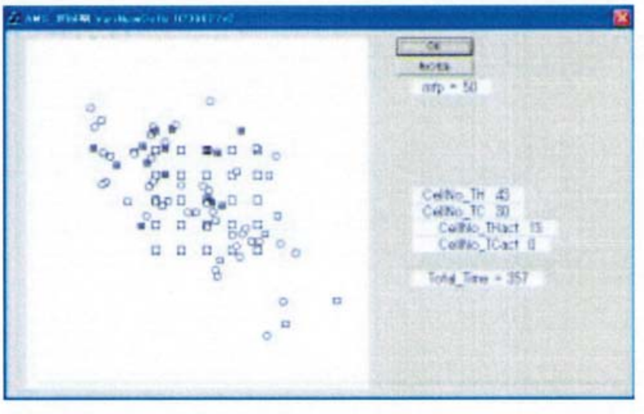
[Simulation results]

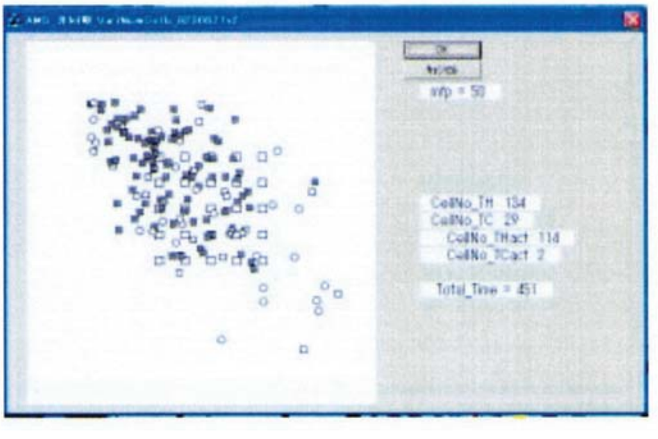
According to the density of T cells [T] which flows into the tumor area, the local ignition occurs when [T] is enough high, but it does not occur when [T] is low.
This means that a healthy condition may attack strongly to the antigen.

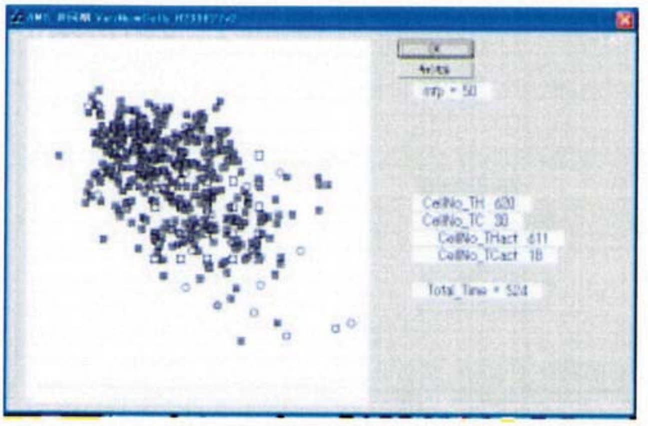
Input data is not actual one.
Symbol explanation
□・・・CD4T cell
▣ ・・・Activated CD4T cell
○・・・CD8T cell
◎・・・Activated CD8T cells
Large □・・・antigen like a tumor peptide
mfp・・・mean free path

(1) The case where [T] flowing into the area is high.
The local ignition exists. The eigen value λ>1.

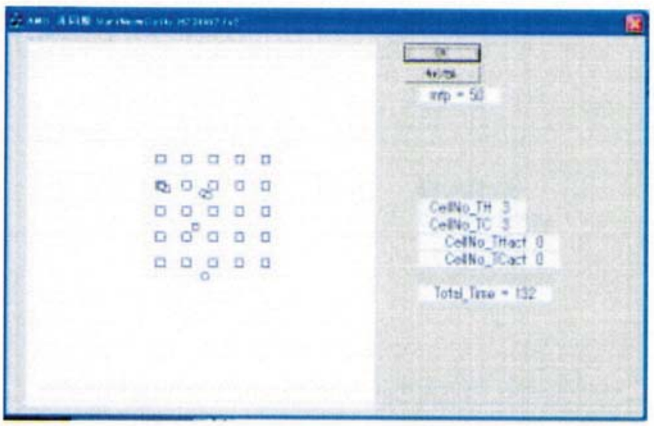


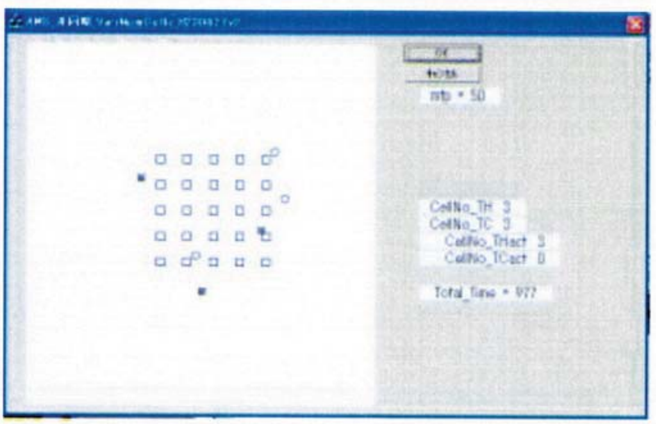


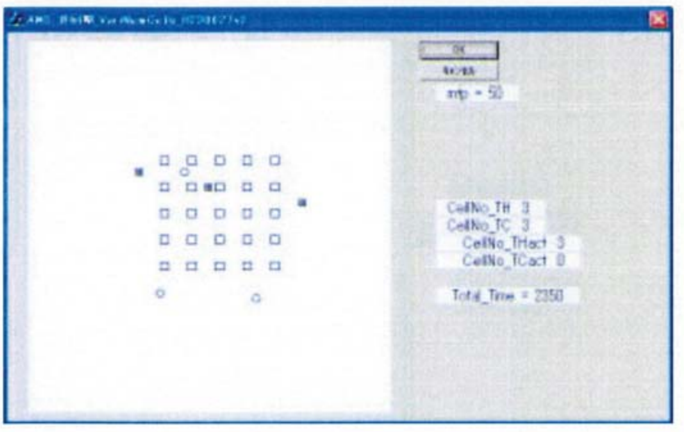




(2) The case where [T] flowing into the area is low.
The local ignition does not exist. The eigen value λ<1.







How this analysis and simulation method should be developed in a future.

[target]Many of events which occurred in treatments and researches actually can be consistent to the analytical results and made understood through the analysis quantitatively.

For this purpose,

(1) The accumulation of cases studied in analytical side and total comprehension about what kinds of behaviors are caused are important.
(2) The increase of the number of situations where analytical results and medical situations with the states of diseases, treatments and the results are consistent will deepen the actual comprehension by analysis.

References
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2. Charles A. Janeway Jr.et. al., Immuno biology the immune system in health and disease, Garland.