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An automatic control mechanism to ignite the immune system locally against a small cancer mass considering reliability

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Abstract

Tumor-immune system interaction is considered. Then it is known that T cells play a main role. There is the detection by each T cell causing T cell activation, and there can be the local ignition of the immune system which I already proposed. While the former can be thought to have a threshold of the activation, the latter has a threshold by the eigen value equal to 1 which causes the local ignition.

Especially the local ignition as a mass action is thought to give a serious damage to healthy tissues if the attack is wrong. On the other hand, it may not be realistic to think that each T cell has an enough reliability to protect healthy cells almost completely from the damage, because the reliability must be very high.

So under the assumption that T cell activation is based on probability, the evaluation way of the reliability in the local ignition is shown. Binomial distribution can be applied .and the evaluation example is also shown.

1. Introduction

Tumor-immune system interaction is considered. Then it is known that T cells play a main role [2]. There should be two steps for a group of T cells to attack. There is the detection of tumor peptides by each T cell causing T cell activation, and there can be theoretically the local ignition of the immune system which I already proposed [1]. While the former can be thought to have a threshold with probability of the activation, the latter has a threshold by the eigen value equal to 1 which causes the local ignition. The realization of these steps is expected to lead to the cure of the tumor.

In this former situation for T cell activation, an affinity between a tumor peptide and a T cell receptor can be thought to be a mechanical pattern matching, and the situation is similar to neural networks [5] although separation between healthy cells and the tumor cells is important in the tumor-immune interaction. But memory T cells are thought to necessarily memorize the antigen patterns.

[Problem and purpose]

(1)Here, the attack against the tumor cells is thought to be conducted through the step of the detection of tumor cells. But at the same time, the protection of healthy cells should be considered. Especially the local ignition as a mass action is thought to give a serious damage to the healthy tissue if the attack is wrong. On the other hand, it may not be realistic to think that each T cell has an enough reliability to protect healthy cells almost completely because the reliability must be very high..

The thresholds and the probabilities, especially the latter one, are expected to be set to give enough high reliability to protect healthy cells thinking natural selection and the evolution.

On the other hand, if we can make the thresholds correspond to the reliability, we can grab the behavior of the immune system more analytically and quantitatively thinking about not only the attack effect, but also the enough reliability for the protection of healthy cells, and may lead the situation of tumor- immune system interaction to the direction of the cure more precisely. If the results of tumor-immune interaction analysis are coherent to the necessity from the result of the reliability analysis, we can be much more confident to the analysis result.

It is known that there are cases where the costimulation of CD4T and CD8T accompanies the CD8T activation to lead to its development to a Tc. Here for the simplicity of the discussion, we analyse only the T cell behaviors which include the cases of the costimulasion.

While the consideration of the costimulation will be expected to heighten the precision to detect an antigen correctly, it will lower the contact probability shown in [1].

The reliability discussed here is very similar to the test of goodness of fit in statistics.

There is necessity for healthy cells to be protected from the local ignition with an enough high reliability.

From these backgrounds, the followings are shown.

(1) Treg cell contributes to the mechanism to make clearer the separation ability between body cells and a tumor peptide like in neural networks. in section 2.1.
(2) The mechanism of the cell-wise detection by T cells and the local ignition as the mass action of the immune system in a local area near the tumor mass is shown in section 2.2.
(3) The model to calculate the reliability is shown in section 3.
(4) The calculation example of the value which leads to the reliability is conducted and shown in section 4

Common notation used is shown here.

[Common notation]

Th ・・・ helper T cell
Tc ・・・ cytotoxic T cell
Tact ・・・ activated T cell
Treg ・・・ regulatory T cell or suppressor T cell
IL2 ・・・ interleukin 2

2. Possibility of local ignition in cytotoxic immune system

The following two steps are necessary to cause local ignition.

（1）T cell activation
（2）Necessity of the local ignition in mass action of multiple T cells

2.1 Activation of T cells

・It is known that a T cell becomes a Treg cell in its development in thymus when the T cell has a big affinity with a peptide of healthy body cells.

In many cases, especially in tumor therapy reports for vaccine therapy, Treg cells tend to work to weaken the therapy effect [3, 4], but at the same time here it is expected that they not only protect healthy cells but also they can make clearer the difference between a tumor peptide and peptides of healthy cells lowering the common part like shown in Fig. 2.

- T cells have aspects to activate based on probability and have its distribution function.
- So here we assume that the activation probability of a T cell is determined by the affinity between the receptors of the T cell and the antigen which is a tumor peptide.

We do not have the data to express the T cell activation curve of probability vs. affinity.

The examples of the curves with expected characters are shown in Fig, 1.

[The possibility of the assumption]

① Mechanical matching situation which depends on mutual locations and directions in the

matching of the receptor and the tumor peptide

② It is known that there are cases where (a) the receptors of T cells have an affinity to an autoantigen which is not zero and is not enough strong (b) the antigen is not enough abundant, but an autoimmune is not caused [2].

③ There is an example of an autoimmune by insulin where an autoimmune is caused by the abundance of insulin [2].

In ② and ③ if the probability of T cell activation according to affinity is not considered, the T cells have only the threshold of the activation to work with the threshold by the eigen value of the local ignition. Then there will be much less difference between a furious immune response and a mild immune response as long as there is no difference among T cell activation levels.

These responses of the immune system are expected to be caused by not only T cells but also the attack by antibodies, etc., so the upper discussion may be not enough to prove the existence of the probabilistic aspect of T cell activation, but the existence of the probabilistic aspect is expected.

2.2 T cells mass action and local ignition

When there is a positive feedback in a system behavior, it can be expressed as an eigen value problem with eigen values and its eigen vectors. The feedback mechanism is shown in Fig 3. The example of this mechanism is shown in detail in [1, 5] where Th, Tc and IL2 are considered..

It is considered that each T cell works through the probability expressed by $\alpha \cdot \beta \cdot \gamma$ in [1, 5].

α ・・・contact probability of a pathogen with a T cell receptor

β ・・・recognition probability of the pathogen by the T cell

γ ・・・deletion probability of the pathogen by the Tc cell with the contact of a tumor cell

For the simplicity of the discussion, α is assumed to be constant in this article.

3. Model to calculate reliability for separation between a tumor peptide and a peptide of healthy cells

[Background]

Qualitatively speaking, it is expected that the total number of Tact cells has a main role to cause the local ignition thinking from the mechanism. In other words, this means that local ignition does not depend on the locations of Tact cells around the mass but the total number of Tact cells around the mass.

We consider $X = (x_1+x_2+\cdots+x_N)/N$. X means the average of the samples $x_1, x_2, \cdots, x_N$, where $x_i = 1$ when T cell i is activated, $x_i = 0$ when T cell i is not activated and x_i has activation probability p and statistical independence.

The total number N varies, and the distribution of $x_1, x_2, \cdots, x_N$ in the mass also varies. These behaviors are expressed as an eigen value problem, and X variation depends on the eigen value, and its abrupt increase depends on the eigen value $\lambda > 1$ which means the local ignition, and the distribution depends on the eigen vector [1].

So $x_1+x_2+\cdots+x_N$ is much concerned with the expression of the behavior of the local ignition as a mass action.

Here we use equation (1) for X. Because the equation (1) is similar to the normalized eigen vector in an eigen value problem, and we think the responses of T cell mass action.

X is expressed by binomial distribution although it is divided by N. The reliability for the separation

between healthy cells and a tumor peptide is determined by the average and the diversion.
The nearer to 1 the average is, the higher the reliability is.
The smaller the divergence is, the higher the reliability is.

・$X = (x_1+x_2+\cdots\cdots+x_N)/N$ ・・・(1)
・The average of X $E(X) = p$
・The diversion of X $\sigma^2(X) = pq/N = p(1-p)/N$ $q = 1-p$
N・・・Total number of T cells in a unit volume in the mass of tumor
P・・・T cell activation probability when the receptors contact to a kind of tumor peptides..
Here, $\sigma^2(X)$ becomes smaller when N becomes larger.

4. Evaluation of reliability by comparison between two cases

At present we can not calculate directly an actual value of reliability mainly because of the lack of necessary data, so here we inspect the effects of the total number of participated T cells near the tumor mass, the affinity and the number of Tact cells by comparison between two cases one of which has an enough high reliability to cause the local ignition without any damage to healthy cells, the other case which can not cause the local ignition.

Here, in the former case, the affinity between the T cell receptor and the tumor peptide is enough high to cause the local ignition, in the other case, the affinity is less high and can not cause the local ignition. We call the former case 2 and the latter case 1.

This relationship is shown in Fig. 4

The probability p of the T cell activation and the total number N of T cells which means the total number of T cells with an affinity of the receptors to a tumor peptide are given about case 1 and case 2 respectively as follows.

Case 1: p_1 and N_1
E_1 ・・・its average
σ_1^2 ・・・its diversion
z_1 ・・・its affinity between the receptor and the tumor peptide

Case2 : p_2 and N_2
E_2 ・・・its average
σ_2^2 ・・・its diversion
z_2 ・・・its affinity between the receptor and the tumor peptide

Here, we conduct the following modifications to make the reliability of case 1 same with that of case 2.

(1) Modification of diversion by change of T cell number in the local area around the tumor mass
The diversion of X is given by equation (2).
$\sigma^2\{X\} = p(1-p)/N$ ・・・・・(2)
Where $0 \leqq X \leqq 1$.

When diversion is smaller, the separation between healthy cells and tumor cell is clearer. Because the reliability becomes higher.

Usually $\sigma_2^2 < \sigma_1^2$ because p_2 is nearer to 1 than p_1.

We can make σ_1^2 nearly same with σ_2^2 by increasing N_1.

(2) Modification of average by change of T cell number in the local area around the tumor mass
The average of X is given by equation (3).
$E(X) = p$ ・・・・・(3)
Where $0 \leqq X \leqq 1$

When the average is larger, the separation between healthy cells and tumor cell is clearer, and the reliability becomes higher.

Usually $E_1 < E_2$ because p_2 is nearer to 1 than p_1.

We can make E_1 nearly same with E_2 by increasing N_1.

(1) Modification to make diversions equal using the total number of T cells

$\sigma_1^2 = \sigma^2(X_1) = p_1(1-p_1)/N_1$

$\sigma_2^2 = \sigma^2(X_2) = p_2(1-p_2)/N_2$

From $\sigma_1^2 = \sigma_2^2$

$p_1(1-p_1)/N_{1a} = p_2(1-p_2)/N_2$

$N_{1a} = N_2 \cdot p_1(1-p_1)/(p_2(1-p_2))$

$= N_2 \cdot (p_1/p_2)\{(1-p_1)/(1-p_2)\}$

(2) Modification using both average and diversion

We conduct modification by $E_1'^2 / \sigma_1^2 = E_2^2 / \sigma_2^2$ where the dimensions are made equal, because both average and diversion affect the reliability of the separation and have different dimensions..

$p_1^2/\sigma^2(X_1) = p_2^2/\sigma^2(X_2)$

$p_1^2/(p_1(1-p_1)/N_{1b}) = p_2^2/(p_2(1-p_2)/N_2)$

$N_{1b} \cdot p_1^2/(p_1(1-p_1)) = N_2 \cdot p_2^2/(p_2(1-p_2))$

$N_{1b} = N_2 \cdot (p_2^2/p_1^2)\{(p_1(1-p_1))/(p_2(1-p_2))\}$

$= N_2 \cdot (p_2/p_1)(1-p_1)/(1-p_2)$

We adopt N_{1b} because of $N_{1b} > N_{1a}$ from $p_2 > p_1$

「The meanings of the results」

(1) When N_1 is increased to N_{1b} , the reliability achieved by both N_{1b} and the affinity of z_1 becomes nearly same with the reliability achieved by both N_2 and the affinity of z_2.

$N_{1b} = N_2 \cdot (p_2/p_1)\{(1-p_1)/(1-p_2)\}$

(2) When N_1 of T cells with the affinity of z_1 is increased to N_{1b}, the number of Tact can be calculated in equation (4).

$N_{1b} \cdot p_1 = (N_2 \cdot p_2) \cdot \{(1-p_1)/(1-p_2)\}$ ····(4)

Equation (4) means that the number of Tact cells with the affinity z_1 is nearly same with the number of Tact with the affinity z_2 although $\{(1-p_1)/(1-p_2)\}$ is multiplied.

「the modified number of Tact with affinity z_1」=「(the number of Tact in case 2)$\cdot\{(1-p_1)/(1-p_2)\}$」

This means that the numbers of Tact in the two cases are almost equal each other to a certain extent after the equalization of the reliabilities.

The meaning of $(1-p_1)/(1-p_2)$ is that when $p_2 = 1$, $\sigma_2^2 = p_2(1-p_2)/N_2 = 0$ There is no error in the ditection, so N_{1b} must be ∞.

$\{(1-p_1)/(1-p_2)\} \to \infty$ when $p_2 \to 1$ because $\sigma_2^2 = p_2(1-p_2)/N \to 0$ when $p_2 \to 1$.

5. Conclusion

The results of the analysis conducted here can be arranged as follows.

(1) The recognition of a tumor peptide by T cells is considered as a separation problem between healthy cells and tumor cells through the tumor peptide

(2) Treg has a function to expand and clarify a difference between healthy cells and tumor cells through the tumor peptide.

(3) The reliability of the separation between healthy cells and tumor cells by probability can be expressed using binomial distribution although it is divided by the total sample number N.

(4) Even if the affinity of T cell receptors to a tumor peptide is weak or T cells are repressed by Treg cells, when the number of the T cells with the same receptors increases, the number of Tact cells

increases getting an enough reliability to be able to achieve the local ignition from the point view of reliability safely.

(5) When the affinity of T cell receptors to a tumor peptide is weaker or T cells are more repressed by Tregs in comparison with the condition of T cells where an enough high reliability is achieved and the local ignition can be caused, the number of the T cells with the same receptor, which has the weak affinity, must be increased to a very large extent to have the same reliability.

References

1. Takase, M. (2010) Induction and application of an equation to analyze a local ignition of the immune system for a complete deletion of a cancer mass. Theory of Biomathematics and its applications VI. RISM 1704, 53-60 Kyoto University.
2. Janeway, C. A., Jr. et al. Immuno biology: the immune system in health and disease. Garland.
3. Zhang, Y. et al. (2006) Th1 cell adjuvant therapy combined with tumor vaccination. International Immunology 19, 151-161
4. Noorth, R. J., and Bursuker, I. (1984) Generation and decay of the immune response to a progressive fibrosarcoma J. Exp. Med. 159, 1290-1311
5. Takase, M. (2009) Cancer and immune system interaction model like a neural network model, analysis of cancer mass effect and meaning of vaccine. Theory of Biomathematics and its applications V. RISM 1663, 35-40 Kyoto University.

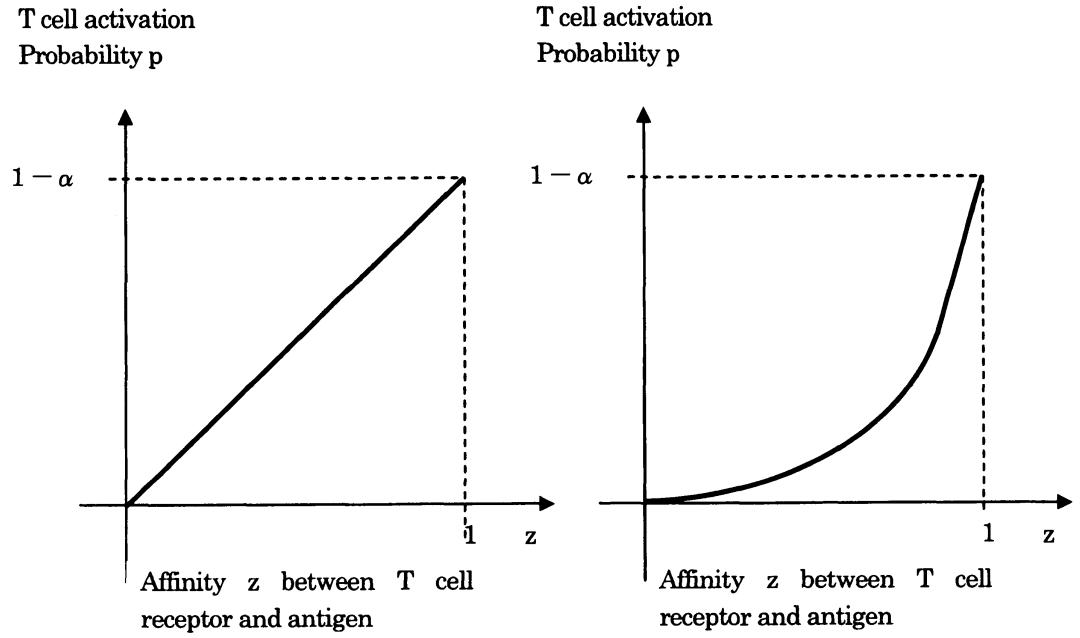


Fig. 1 The graphs of T cell activation probability vs. affinity between T cell receptor and antigen

As meanings of α the following two cases are considered.

(1) When the affinity is 1 and near to a peptide of healthy cells, α means the inhibition by Treg cells.

(2) α means a little displacement of T cell receptor from the maximum fitting when we assume the existence of the maximum mechanical fitting even if the affinity is 1.

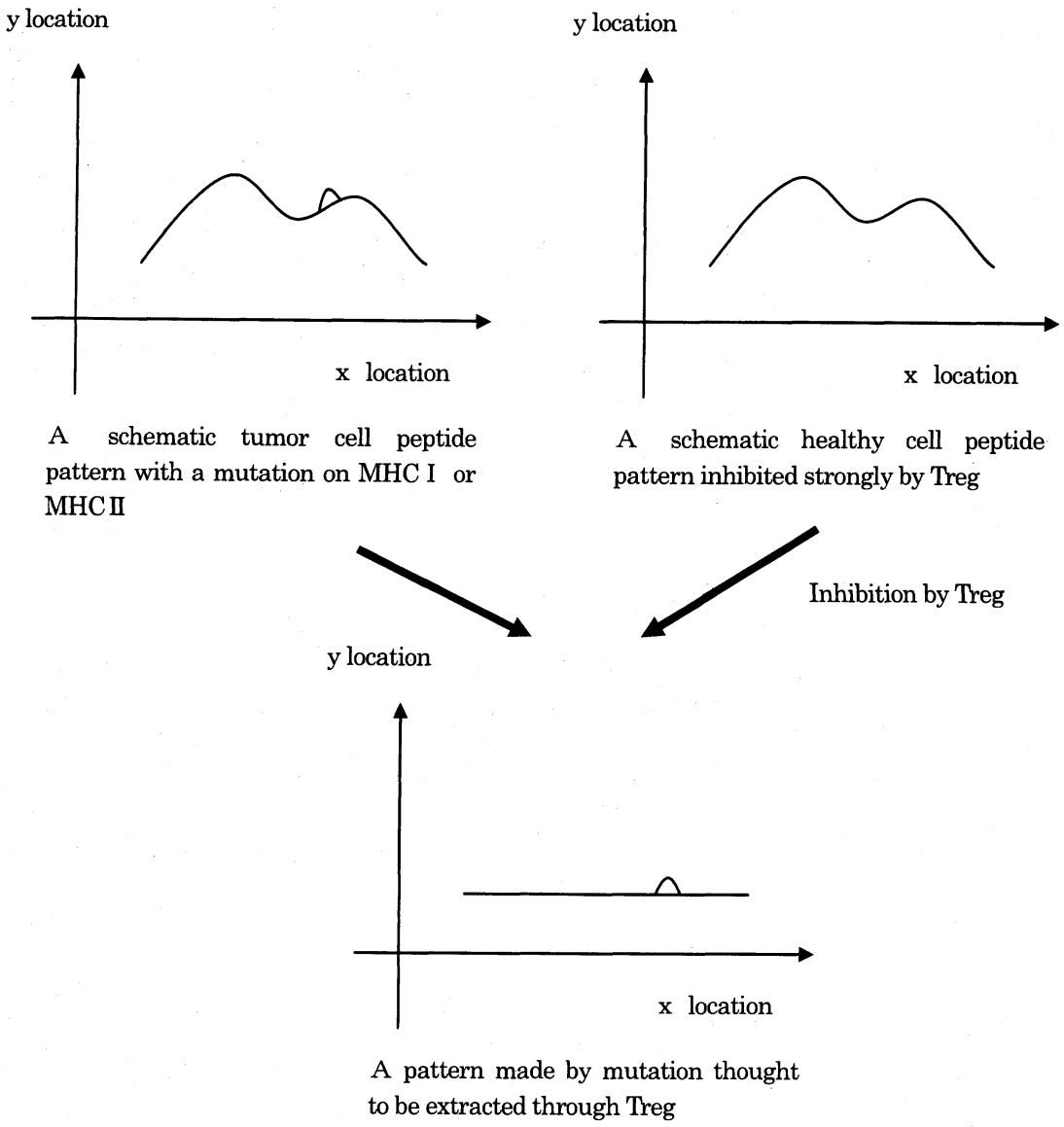
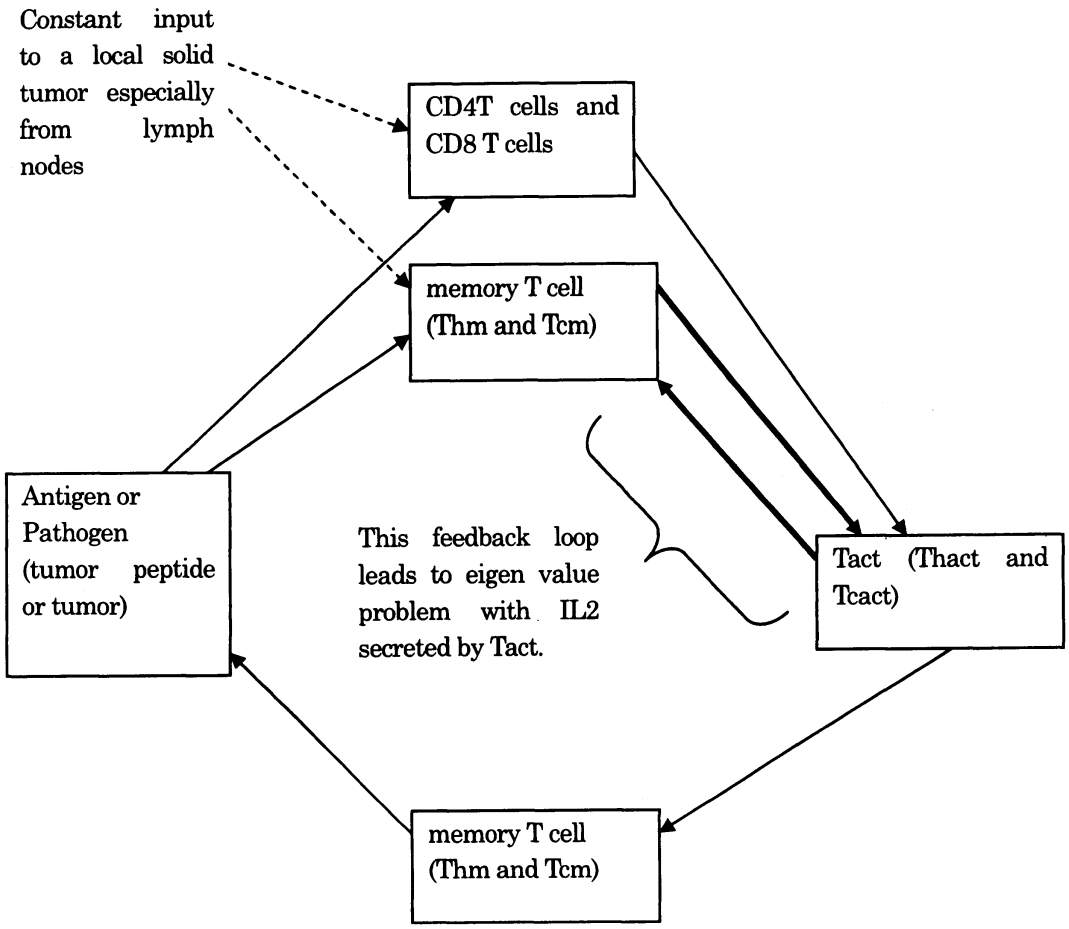


Fig. 2 Mechanism to make the difference between a tumor peptide and that of healthy cells by deleting the common and similar part



About why eigen value can be applied

Fig.3 An example of mechanism to cause the local ignition

Thact ・・・activated CD4 T cell
Tcact ・・・activated CD8 T cell
Thm ・・・memory CD4 T cell
Tcm ・・・memory CD8 T cell

It is considered that each T cell works through the probability expressed by $\alpha \cdot \beta \cdot \gamma$ where the meanings of α, β and γ are shown in section 2.2.

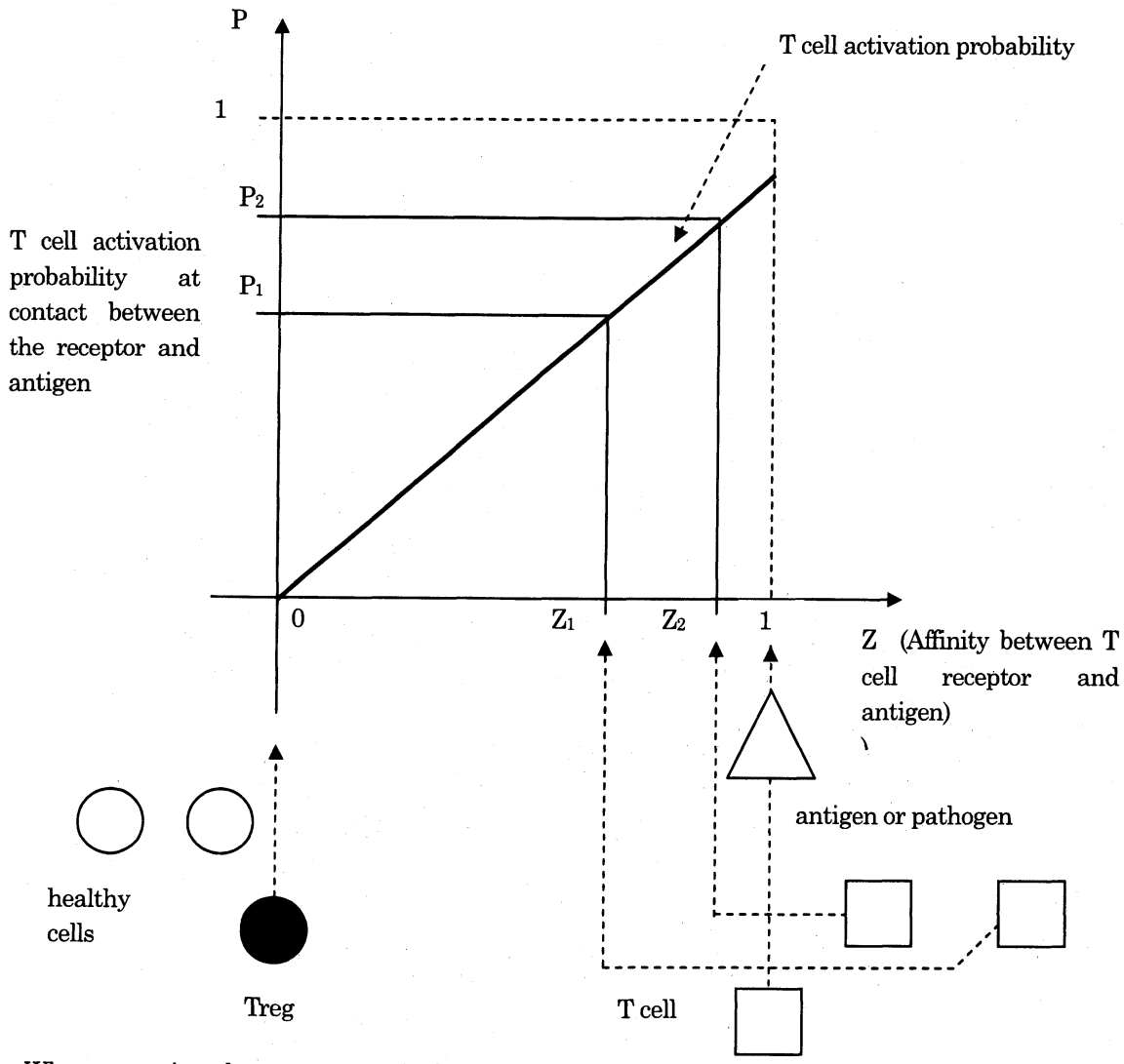


Fig. 4 Relationship of T cell activation probabilities by affinity z_1, z_2

T cell activation probabilities by affinity z_1, z_2 are p_1 and p_2 respectively, but the contact probability is assumed to be constant.