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Potential mechanisms of relapse in autoimmune disease

By

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Abstract

The mechanisms of autoimmune disease have remained puzzling for a long time. For example, many human autoimmune diseases are characterized by relapse, although animals often spontaneously recover from autoimmunity. Here we will investigate the potential mechanism of relapse in terms of mathematical model.

§ 1. Introduction

The mechanism of autoimmune disease is said to be very complex. However, in this study, we will propose a simple mathematical model characterized by two functions, "target cell growth" and "personal immune response". We will show that these two functions capture the essence of the mechanism and can explain many of the symptom dynamics observed for autoimmune disease.

Autoimmune disease occurs when the immune system is fooled into attacking 'self'. Almost any organ or tissue in the body represents 'self' and can therefore be a target for autoimmune destruction [5], [11]. Many autoimmune diseases involve specific target cells or organs, such as pancreatic β-cells being destroyed in insulin-dependent diabetes mellitus type-1 (IDDM) or the destruction of axonal myelin sheaths in multiple sclerosis (MS) [7], [10], [11]. Interestingly, it is said that the symptom of IDDM represents chronic

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but one of MS represents relapse [5], [7], [11]. Although animals often spontaneously recover from autoimmunity, many human autoimmune diseases are characterized by relapse. It has been suggested that the relapses are caused by the stimulation of newly recruited T cells reactive to spreading determinants (in fact, relapse in experimental autoimmune encephalomyelitis do not require spreading determinants, but can be driven by T cells reactive to the initial dominant of myelin basic protein) [1]. Thus humans and animals can develop various autoimmune diseases and represent relapse of symptoms. For more detailed discussion of autoimmune disease, see [6].

Several hypotheses (sequestered antigen, cross-reaction, superantigen and so on) have been proposed to explain the development of autoimmunity and subsequent disease in humans and animals (see [3], [7], [10]). These hypotheses are very complex but, briefly, autoimmunity develops when a specific immune response for an autoantigen is induced. Usually a specific immune response for a foreign antigen (adaptive immune response) excludes the antigen from the body. However, once a specific immune response for an autoantigen is induced, it is impossible for the immune system to completely exclude that autoantigen from the body. Therefore, the autoaggressive immune reaction is amplified because the autoantigens continue to be produced and so further induce the autoaggressive immune reaction. Thus autoimmune disease develops. Autoimmunity is said to start from T cell reactions and the activation of immune cells such as cytotoxic T lymphocytes and helper T cells (which activate B cells or macrophages and thus induce antibodies) is caused by tissue injury. In this paper, we will investigate the potential mechanism of relapse.

§ 2. Model

We briefly explain the vicious circle of autoimmunity. An existing cell in vivo becomes a key effector cell by some chance event that initiates autoimmune disease. Next this key effector cell attacks and damages a healthy cell. At this stage, the protein of the damaged cell (antigen) is captured by an antigen presenting cell (APC) such as a dendritic cell (DC), B cell or macrophage and the protein is shown as a self-antigen at the lymph vessel. Then the immune cells which are specific to the protein are induced, and these specific immune cells attack and damage more healthy cells resulting in a vicious circle of autoimmunity (see Fig.1). Thereafter autoimmune disease develops because our immune system cannot completely exclude the self-antigen from the body

and the autoaggressive immune reaction is amplified. Although this interpretation of the vicious circle of autoimmunity is incomplete, it is not unnatural and we use it as a basis for our mathematical model. For example, virus-induced cross-reactive immune

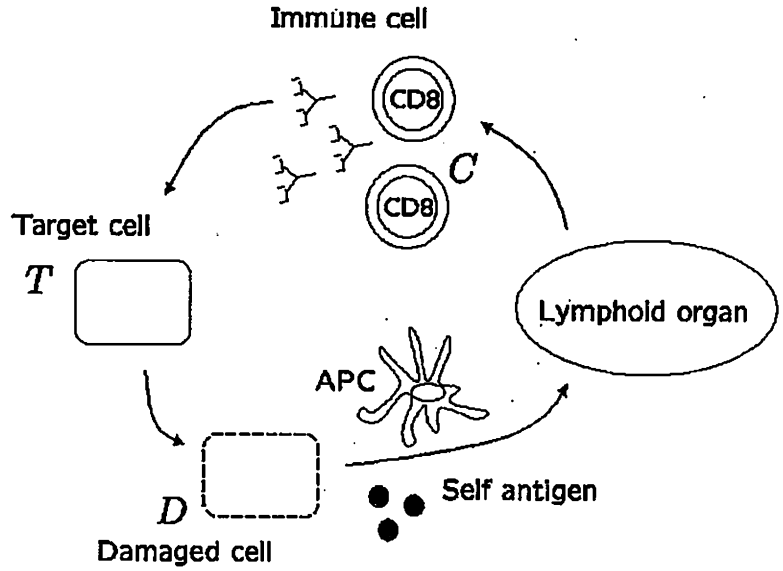

Figure 1. A vicious cycle of autoimmunity

cells can also become the key effector cells [2], [5], [11], [12]. In this way, virus infection have long been associated with the exacerbation of autoimmune disease (however, there is also evidence that viruses can actually protect against autoimmune disease [4]).

To simplify the model we assume that cells damaged by key effector cells already exist and we do not consider the dynamics of key effector cells (this is our future work). Moreover we assume that the number of APCs remains at a constant low level and so we do not consider APC dynamics (Wodarz at el. assumed that APCs such as DCs are variables [13]). Then, combining the dynamics of immune cells and target cells (healthy cells), we obtain a basic model of autoimmune disease dynamics:

$$
\begin{aligned}
T' &= g(T) - \beta_1 TC, \\
D' &= \beta_1 TC - \alpha D, \\
C' &= f(D) - \gamma C
\end{aligned}
\tag{2.1}
$$

where $g(T)$ is a function of T and $f(D)$ is a function of D. This model has three variables, the population size of target cells (T), damaged cells (antigens D) and immune cells (C). Target cells, damaged cells, immune cells die at rate μ (see below), α, γ, respectively. The parameter β describes the efficacy of the damage process and includes the rates at which immune cells find target cells and immune cells succeed in attacking target cells. Thus βTC can be viewed as the force of damage by immune cells. The immune system in vivo is more complex than our assumption. For more detailed discussion of this simple model, see [6].

§ 3. Relapse of autoimmune disease

Several autoimmune diseases such as MS and Experimental Autoimmune Encephalomyelitis (EAE) are characterized by relapse. EAE has been studied extensively to elucidate the pathomechanism of MS. Using the EAE model, many groups investugated the mechanism of relapse and report factors that are related to this phenomenon. Among them, epitope spreading is one of the most fascinating explanations. However the mechanisms are not known. Here we will propose the potential mechanism of this phenomenon in terms of our simple mathematical model.

§ 3.1. Target cell growth function

The differences resulting from the internal organs or tissues which initiate each autoimmune disease (for example, MS, RA, SLE and so on) are represented by the target cell growth function $g(T)$. We consider that the functional forms of target cell growth in humans are given by the following reasonable function, $g(T)$;

$$g(T) = \lambda - \mu T + pT(1 - \frac{T}{L}).$$

Previously, $g(T)$ has been investigated by Perelson *et al.* (see [9]) in models for HIV infection. In this function the parameter λ is the rate at which new target cells are produced within the body and μ is death rate of target cells (note that α is larger than μ because of the damage). The last term (a logistic part) implies that target cells can also be created by proliferation of existing target cells. Here we represent the proliferation by a logistic function in which p is the maximum proliferation rate and L is the target cell population density at which proliferation shuts off. Note that target cell growth function, $g(T)$, is density dependent. This implies limitation of spatial

capacity or nutrition in vivo. The interested reader is also referred to [8] and [9]. An alternative function including density dependence, $g(T,D) = \lambda - \mu T + pT(1 - (T+D)/L)$, has been investigated by Liancheng Wang *et al.* (see [14]). However, according to numerical simulations, the difference in the functional form does not change the qualitative behavior of system (2.1) with $g(T)$. Therefore, to avoid mathematical difficulty, we assume that the functional form which includes density dependence is $g(T)$. In order to investigate the effect of this target growth function, we assume that $f(D) = kD$. The parameter k can be regarded as the (per damaged cell) average magnitude of activation of immune response by APCs. In this linear functional response the number of immune cells induced by APCs is proportional to the number of damaged cells. Thus kD can be viewed as the proliferation rate of immune cells by APCs at time t.

We express the population dynamics of target cells by $g(T) = \lambda - \mu T + pT(1 - T/L)$ to obtain the model:

$$
\begin{aligned}
T' &= \lambda - \mu T + pT(1 - \frac{T}{L}) - \beta TC, \\
D' &= \beta TC - \alpha D, \\
C' &= kD - \gamma C.
\end{aligned}
\tag{3.1}
$$

This model is also the same as an HIV model ([8],[9]). So we only consider the implications for autoimmune disease.

We found numerical solutions of (3.1) with parameters $\lambda = 0.1$, $p = 3$, $\mu = 0.1$, $\beta = 0.5$, $\alpha = 1.1$, $\gamma = 0.1$, $L = 100$, (i) $k = 0.001$, (ii) $k = 0.01$, (iii) $k = 0.1$ and (iv) $k = 1$ (Fig.2). Note that target cells propagate themselves because $p - \mu > 0$. Fig.2 (i) shows tolerance of the immune response. Fig.2 (ii) shows slow progression of the disease and mild symptoms, which means that target cells gradually decrease but there is a relatively high level of target cells in the chronic phase. Fig.2 (iii) shows relapse of autoimmune disease. Fig.2 (iv) shows rapid progression of the disease and severe symptoms, which means that target cells suddenly decrease and there exist only a few target cells in the chronic phase. Fig.2 (iii) is very interesting because disease symptoms are periodic. This pattern corresponds to relapse of autoimmune disease and can be observed for the case of multiple sclerosis and so on ([13]). Intuitively, the reason for the occurrence of this relapse pattern can be explained as follows: If k is relatively small and the number of target cells is small, then the number of target cells increases because of the logistic nature of g. Then there is an associated increase in damaged

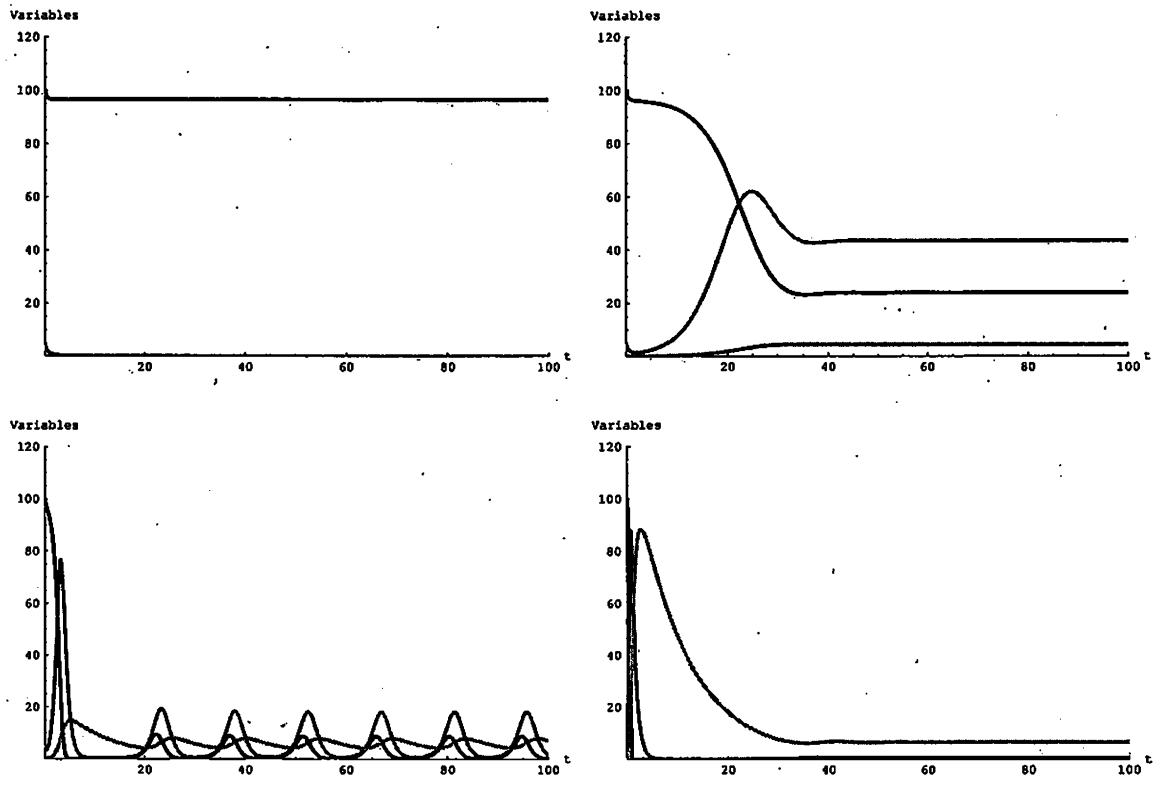

Figure 2. (i) $k = 0.001$: tolerance. (ii) $k = 0.01$: slow progression and mild symptoms. (iii) $k = 0.1$: relapse. (iv) $k = 1$: rapid progression and severe symptoms.

cells and immune cells. The immune cells attack target cells and cause a decrease in the number of target cells and the cycle repeats. Consequently, the effect of target cell growth function may be a cause of the relapse symptom of autoimmune disease.

From mathematical point of view, system (3.1) is interesting since a positive equilibrium point can be unstable. Leenheer *et al.* investigated this system in [8]. It has two equilibria:

$$\bar{E}_0 = (\bar{T}_0, 0, 0), \qquad \bar{E}_+ = (\bar{T}_+, \bar{D}_+, \bar{C}_+)$$

and basic reproductive number $\bar{R}_0 = \beta k \bar{T}_0 / \alpha\gamma$ where $\bar{T}_0$ is given by

$$\bar{T}_0 = \frac{L}{2p}\left((p-\mu) + \sqrt{(p-\mu)^2 + \frac{4p\lambda}{L}}\right).$$

They showed that if $\bar{R}_0 < 1$ then $\bar{E}_0$ is GAS and if $R_0 > 1$ then $\bar{E}_+$ is GAS under certain conditions but $\bar{E}_+$ can be unstable under certain conditions ([8]). In this system, if $\bar{E}_+$

is locally asymptotically stable (LAS) then numerical simulations suggest that $\bar{E}_+$ is probably GAS. However, it is important to note that density dependent growth of target cells can destabilize $\bar{E}_+$ and a stable limit cycle exists ([8]).

§ 3.2. Immnune response function

Although the mechanism is not yet completely understood we can investigate the relationship between immune cell inducement and the symptoms of autoimmune disease by defining the immune response function $f(D)$. In order to investigate the effect of this immune response function, we assume that $g(T) = \lambda - \mu T$. Different people may have different immune response functions (one can investigate the personal immune response function experimentally) or the personal immune response function may depend on the kind of immune cells or patient's condition. However a reasonable function, $f(D)$, for immune cell inducement is considered as follws; if there exist only a few antigens then APCs do not induce immune cells, but if there exist relatively many antigens then immune cells are gradually induced and the proliferation of immune cells is saturated for sufficiently many antigens. Therefore, we will investigate the qualitative behavior of the system for the following immune response function, $f(D)$ given by,

$$f(D) = \frac{mD^2}{h^2 + D^2}.$$

The parameter m can be regarded as the maximum proliferation rate of immune cells caused by APCs. Moreover h is the number of damaged cells (because the antigen is produced by damaged cells) at which the proliferation of immune cells is half of the maximum m. Thus $mD^2/(h^2 + D^2)$ can be viewed as the proliferation rate of immune cells by APCs. This functional response, $f(D)$, is justified immunologically because APCs hardly induce immune cells when only a few antigens exist. Although the mechanism by which immune cells are induced is still not clear, a nonlinear personal immune response function, $f(D)$, is biologically reasonable.

We express the population dynamics of immune cells by $f(D) = mD^2/(h^2 + D^2)$ to obtain the model:

$$\begin{aligned} T' &= \lambda - \mu T - \beta TC, \\ D' &= \beta TC - \alpha D, \\ C' &= \frac{mD^2}{h^2 + D^2} - \gamma C. \end{aligned} \tag{3.2}$$

In [6], we concluded that this system do not explain the relapse with $\mu \geq \gamma$. However, we found that this system can explain the relapse if $\mu < \gamma$. That is, the effect of immune response function may be a cause of the relapse symptom of autoimmune disease.

We show that some equilibrium becomes unstable by Hopf bifurcation. This system has three equilibria:

$$\hat{E}_0 = (\hat{T}_0, 0, 0), \quad \hat{E}_+ = (\hat{T}_+, \hat{D}_+, \hat{C}_+), \quad \hat{E}_- = (\hat{T}_-, \hat{D}_-, \hat{C}_-).$$

In particular, we can show that $\hat{E}_0$ is always stable. From a direct calculation, the coordinates of $\hat{E}_\pm$ are given by

$$\hat{T}_\pm = \frac{\gamma\alpha(h^2 + \hat{D}_\pm^2)}{\beta m \hat{D}_\pm}, \quad \hat{C}_\pm = \frac{m\hat{D}_\pm^2}{\gamma(h^2 + \hat{D}_\pm^2)}$$

and $\hat{D}_\pm$ are the roots of the following equation:

$$\alpha(\mu\gamma + \beta m)D^2 - \lambda\beta m D + \mu\gamma\alpha h^2 = 0.$$

In particular, $\hat{D}_\pm$ is given by

$$\hat{D}_\pm = \frac{\lambda\beta m \pm \sqrt{\lambda^2\beta^2 m^2 - 4\mu\gamma\alpha^2 h^2(\gamma\mu + \beta m)}}{2\alpha(\mu\gamma + \beta m)}.$$

Remark that the exsistence condition of $\hat{E}_\pm$ is

$$\lambda^2\beta^2 m^2 - 4\mu\gamma\alpha^2 h^2(\mu\gamma + \beta m) > 0.$$

The Jacobian matrix of (3.2) at $\hat{E}_\pm$ is

$$J(\hat{E}_\pm) = \begin{bmatrix} -\mu - \beta\hat{C}_\pm & 0 & -\beta\hat{T}_\pm \\ \beta\hat{C}_\pm & -\alpha & \beta\hat{T}_\pm \\ 0 & \dfrac{2mh^2\hat{D}_\pm}{(h^2 + \hat{D}_\pm^2)^2} & -\gamma \end{bmatrix}.$$

The characteristic equation of $J(\hat{E}_\pm)$ is

$$s^3 + a_1 s^2 + a_2 s + a_3 = 0$$

where

$$\begin{aligned} a_1 &= \alpha + \gamma + \mu + \beta\hat{C}_\pm, \\ a_2 &= \alpha\gamma + (\mu + \beta\hat{C}_\pm)(\alpha + \gamma) - \frac{2\gamma\alpha h^2}{h^2 + \hat{D}_\pm^2}, \\ a_3 &= (\mu + \beta\hat{C}_\pm)\alpha\gamma - \frac{2\gamma\mu\alpha h^2}{h^2 + \hat{D}_\pm^2}. \end{aligned}$$

Here s denotes the indeterminate of the polynomial. Therefore from Routh-Hurwitz criteria, all eigenvalues have negative real parts if and only if

$$a_1 > 0,\ a_3 > 0,\ a_1a_2 - a_3 > 0.$$

From a direct calculation, we can show that $\hat{E}_-$ is always unstable if it exists and $a_3 > 0$ for $\hat{E}_+$. Finally, we investigate whether $a_1a_2 - a_3 > 0$ or not. In fact, we can show $a_1a_2 - a_3 > 0$ under some conditions. For example, we can calculate as follows:

$$\begin{aligned} a_1a_2 - a_3 &= (\alpha+\gamma)\{\alpha\gamma + (\mu+\beta\hat{C}_+)(\alpha+\gamma) + (\mu+\beta\hat{C}_+)^2\} - \frac{2\alpha\gamma h^2}{h^2+\hat{D}_+^2}(\alpha+\gamma+\beta\hat{C}_+) \\ &> (\alpha+\gamma)\{\alpha\gamma + (\mu+\beta\hat{C}_+)(\alpha+\gamma) + (\mu+\beta\hat{C}_+)^2\} - 2\alpha\gamma(\alpha+\gamma+\beta\hat{C}_+) \\ &= (\alpha+\gamma)\{\alpha(\mu-\gamma) + \mu\gamma + (\mu+\beta\hat{C}_+)^2\} + \beta\hat{C}_+(\alpha^2+\gamma^2). \end{aligned}$$

Therefore, if $\mu \geq \gamma$, then $a_1a_2 - a_3 > 0$. Similarly, if $\mu \geq \alpha$, then $a_1a_2 - a_3 > 0$. Furthermore, we can calculate

$$\begin{aligned} a_1a_2 - a_3 &> (\alpha+\gamma)\{\alpha\gamma + (\mu+\beta\hat{C}_+)(\alpha+\gamma) + (\mu+\beta\hat{C}_+)^2\} - 2\alpha\gamma(\alpha+\gamma+\beta\hat{C}_+) \\ &= (\alpha+\gamma)\{\alpha\gamma + (\mu+\beta\hat{C}_+)(\alpha+\gamma) + (\mu+\beta\hat{C}_+)^2\} \\ &\quad - \alpha\gamma\{(\alpha+\gamma) + (\alpha+\gamma-2\mu)\} - 2\alpha\gamma(\mu+\beta\hat{C}_+) \\ &= (\alpha+\gamma)(\mu+\beta\hat{C}_+)^2 + (\mu+\beta\hat{C}_+)(\alpha^2+\gamma^2) + \alpha\gamma(2\mu-\alpha-\gamma). \end{aligned}$$

Therefore, if $\mu \geq (\alpha+\gamma)/2$, then $a_1a_2 - a_3 > 0$. That is, if $\mu \geq \gamma$, $\mu \geq \alpha$ or $\mu \geq (\alpha+\gamma)/2$, then $\hat{E}_+$ is always stable whenever it exists.

In [6], we have considered that this system keeps its stability for any parameter set. But we find a parameter set which can destabilize our system. We show some detailed investigations around the following parameter set; $(\lambda,\ \beta,\ \mu,\ \alpha,\ \gamma,\ m,\ h) = (1,\ 1,\ 0.04,\ \alpha \in [0,\ 4],\ \gamma \in [0,\ 16],\ 1,\ 1)$.

Firstly, we investigate the sensitivity of stability for parameter α under a fixed $\gamma = 0.5$. The following figures show the sing of $a_1a_2 - a_3$ and $\lambda^2\beta^2m^2 - 4\mu\gamma\alpha^2h^2(\mu\gamma + \beta m)$, respectively. Fig.3 (i) shows the stability condition of $\hat{E}_+$ whenever it exists and (ii) shows the existence condition of $\hat{E}_+$. In this case, a critical value which can lead to Hoph bifurcation is $\alpha_c \approx 2.16$. If α exceeds this critical value, then $\hat{E}_+$ can be unstable and we can observe some periodic orbit (see (iii) of Fig.4). For several α, we can get snap

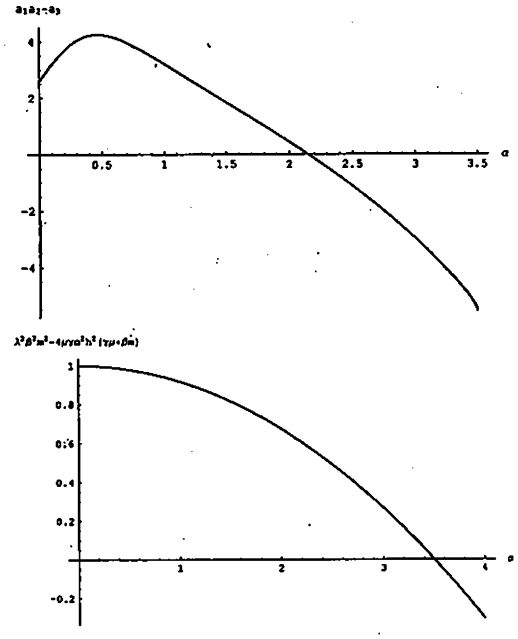

Figure 3. (i) A sign of $a_1a_2 - a_3$ (ii) A sign of $\lambda^2\beta^2m^2 - 4\mu\gamma\alpha^2h^2(\mu\gamma + \beta m)$

shots in Fig.4 ($T(0) = 100$, $D(0) = 1$, $C(0) = 0$). When the death rate of damaged cell, α, is small, then $\hat{E}_+$ is LAS. However $\hat{E}_+$ can be destabilized. For example, if we change α from 2.16 to $2.21375\cdots$, the amplitude of the periodic orbit increases as α increases (see (iii)-(v)). Furthermore, once its value over the value ($\alpha = 2.21375\cdots$), the periodic orbit vanishes (see (vi)). Instinctively, since the amplitude of the periodic orbit increases as α increases and it crosses the stable manifold of $\hat{E}_0$, the periodic orbit vanishes and the orbit converges to $\hat{E}_0$. When we pay attention to the trajectories of each component, we can find the size of immune cell approaches to zero (see Fig.5). Remark that Fig.5 (i) and (ii) correspond to Fig.4 (v) and (vi), respectively.

Next, we investigate the sensitivity of stability for parameter γ under a fixed $\alpha = 0.5$. The following figures show the sing of $a_1a_2 - a_3$ and $\lambda^2\beta^2m^2 - 4\mu\gamma\alpha^2h^2(\mu\gamma + \beta m)$, respectively. Fig.6 (i) shows the stability condition of $\hat{E}_+$ whenever it exists and (ii) shows the existence condition of $\hat{E}_+$. In this case, a critical value which can lead to Hoph bifurcation is $\gamma_c \approx 14.1$. If γ exceeds this critical value, then $\hat{E}_+$ can be unstable. For several γ, we can get snap shots in Fig.7 ($T(0) = 100$, $D(0) = 1$, $C(0) = 0$). In this parameter range, $\hat{E}_+$ is LAS. However the orbit converges not $\hat{E}_+$ but $\hat{E}_0$ in Fig.7

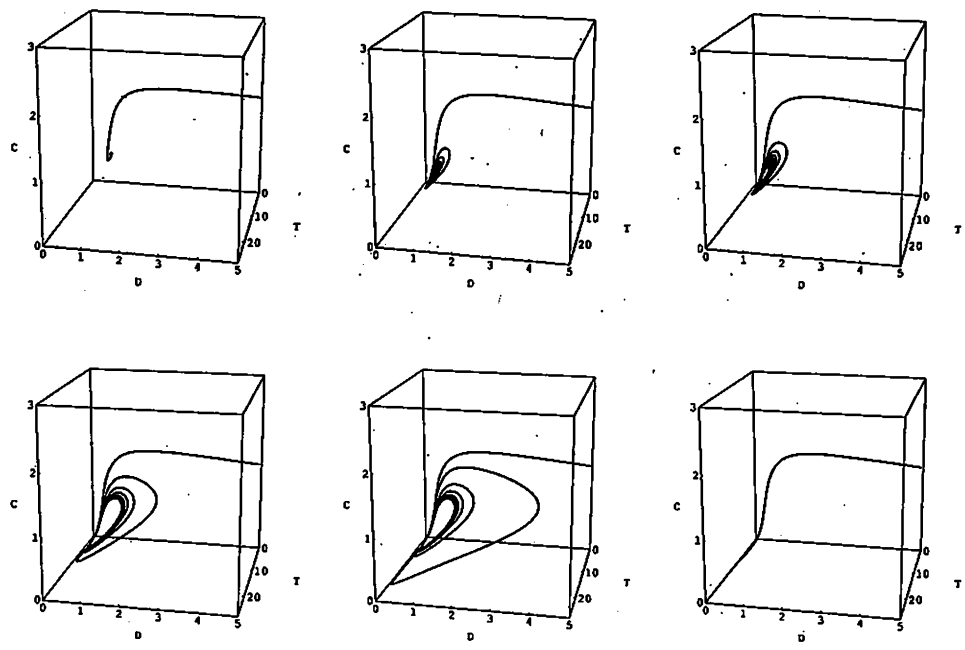

Figure 4. (i) $\alpha = 1.5$: $\hat{E}_+$ is LAS (ii) $\alpha = 2.1$: $\hat{E}_+$ is LAS (iii) $\alpha = 2.16$: $\hat{E}_+$ is unstable (iv) $\alpha = 2.213$: $\hat{E}_+$ is unstable (v) $\alpha = 2.21375$: $\hat{E}_+$ is unstable. (vi) $\alpha = 2.23$: $\hat{E}_+$ is unstable

(iii). Similarly, since the amplitude of the orbit increases as γ increases and it crosses the stable manifold of $\hat{E}_0$, the orbit converges to $\hat{E}_0$. Therefore, even if $\hat{E}_+$ is unstable, we can't observe some periodic orbit under this initial value. However, if we choose the another initial value $T(0) = 14.1384$, $D(0) = 0.868928$, $C(0) = 0.0307294$ which is near $\hat{E}_+$. We can get Fig.8:

These figures imply that the orbit crosses the stable manifold of $\hat{E}_0$ and converges to $\hat{E}_0$ although it seems to approach some periodic attractor once. But in fact, periodic attractor may not exist if it connects the stable manifold of $\hat{E}_0$. Or the periodic orbit may be unstable because of sub-critical Hopf bifurcation. Anyway (3.2) has complicated mathematical structures under some parameter sets. The detailed analysis of mathematical structures is our future works.

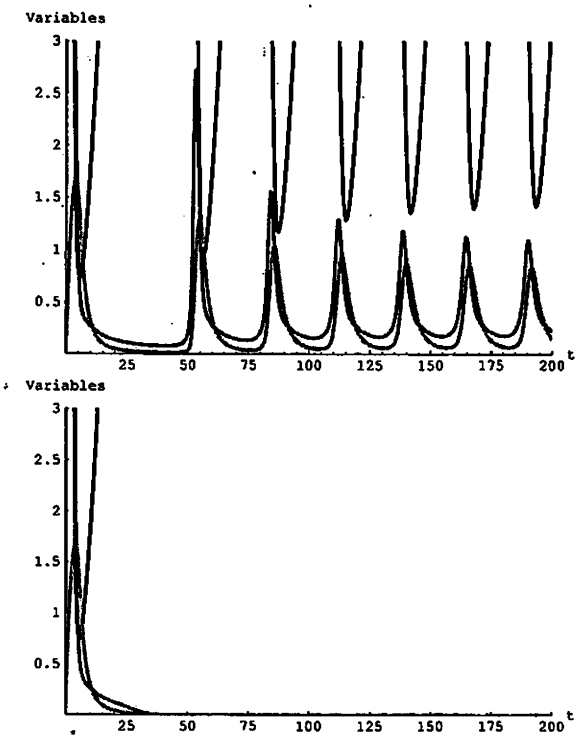

Figure 5. The trajectories of each component:(i) $\alpha = 2.21375$ (ii) $\alpha = 2.23$

Consequently, the decay rate of dameged cell is very important factor for the relapse of the autoimmune disease but one of immune cell seems to be not important because of Fig.4 and 7. In terms of therapy, an increasing of immune cell decay rate is effective for control of the relapse by X-ray treatment. On the other hand, the increasing of damaged cell decay rate may be a cause of the relapse.

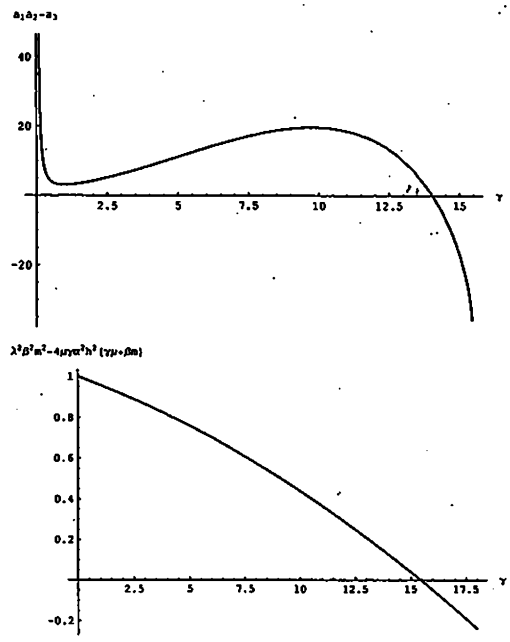

Figure 6. (i) A sign of $a_1a_2 - a_3$ (ii) A sign of $\lambda^2\beta^2m^2 - 4\mu\gamma\alpha^2h^2(\mu\gamma + \beta m)$

§ 4. Discussion

In this paper we have investigated the role of some functional form for the personal immune response function, $f(D)$, and target cell growth function, $g(T)$, in the mechanism of autoimmune disease. The form of these functions dramatically changes the symptoms of autoimmune disease and the mathematical structure of the dynamics. This implies that it is important for us to interpret the phenomena associated with these functions in order to understand the mechanism of autoimmune disease. It has been shown that a nonlinear target cell growth function, $g(T) = \lambda - \mu T + pT(1 - T/L)$, can induce relapse of autoimmune disease. When the number of target cells is small, target cells can increase by the multiplication of the logistic term of $g(T)$. We think the difference of target cell growth functions corresponds to the differences between internal organs which initiate autoimmune disease. And also the immune response function, $f(D) = mD^2/(h^2 + D^2)$, can induce relapse of autoimmune disease. The nonlinear function, $f(D)$, means that when few antigens exist, APCs do not present the antigens and immune cells are hardly induced. Thus the personal immune response functions are closely related to the symptoms of autoimmune disease. This suggests that symptoms of autoimmune disease are different among different people since each person may have a different personal immune response function. Therefore, in the therapy of autoimmune disease we may have to investigate the target cell growth function of each internal organ and the personal immune response function for each patient.

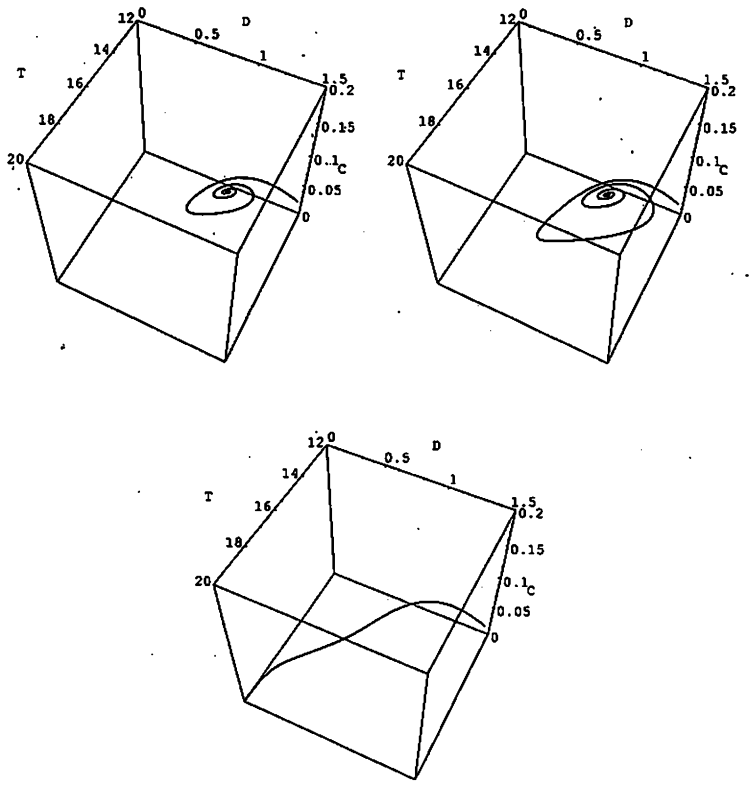

Figure 7. (i) $\gamma = 13.3$: $\hat{E}_+$ is LAS (ii) $\gamma = 13.4$: $\hat{E}_+$ is LAS (iii) $\gamma = 13.5$: $\hat{E}_+$ LAS

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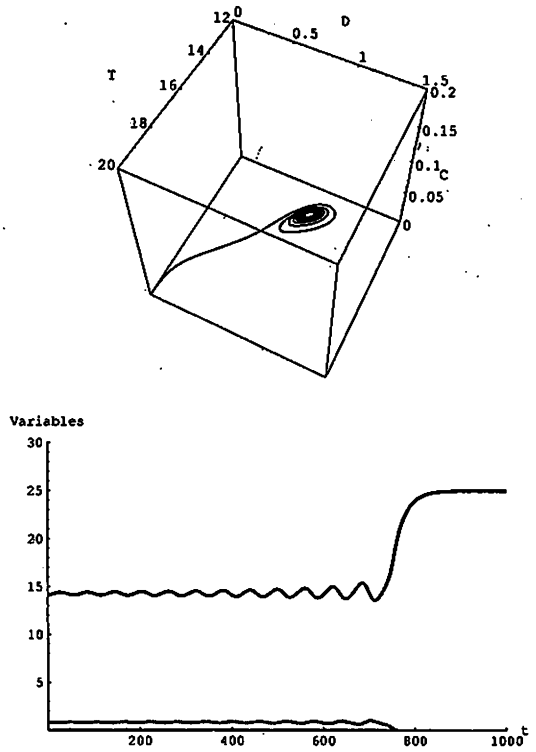

Figure 8. (i) $\gamma = 14.1$: $\hat{E}_+$ is unstable (ii) The trajectory of each component

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