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Global Dynamics of B Cells and Anti-Idiotipic B Cells and its Application to Autoimmunity

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Global behavior of B models is discussed. When the source term for new B cells equals zero, the system has a conservation quantity. It implies the structurally unstability. It suggests that lack of the source of new B cells may unstabilize the immune system. When the B model incorporates autoimmunity, it loses symmetry. The asymmetry suggests the transition from a tolerant state to autoimmune state is more likely than the inverse transition. Effect of dose of antigen is also considered.

Key words: B model, global dynamics, conservation quantity, autoimmunity

1. Introduction

In this paper, we consider the qualitative analysis of B cell models for an application to autoimmune disease.

De Boer, Perelson, and Kevrekidis [1] consider the behavior of immune network interaction with various kinds of models. One of them is the B model, which describes the interaction between B cell clones. It is one of the simplest models and is used as a measure of more complicated models, for example, the AB model, which incorporates the antibodies as well as the B cells. B models are investigated also in [3], for example. Perelson and Weisbuch [2] deal with mathematical models in immunology, which include B models and AB models.

Sulzer and van Hemmen [4] consider a strategy to treat autoimmunity. They consider the effect of controlled dose of antigen using the models based on the AB models. They suggest that repeated injection of antigen according to monitored autoantibody titer is effective to the transit from an autoimmune state to a tolerant state, or the healthy state.

In this paper, we consider a situation similar to that of [4]. We here use B models instead of AB models. Since B models are simple, we can deal with them rigorously, and the observation of the phase space is clear.

In Section 2, we introduce B models and its application to autoimmunity.

In Section 3, we consider the qualitative analysis of the B models with two clones. We mainly deal with the cases where there are no recruitment of new B cells. In these cases, the system has a conservation quantity. We can prove the existence of homoclinic, heteroclinic, and periodic orbits using the conservation quantity. We compare the B model with autoimmunity to that without it. The

flow of the former is more complicated than the latter. The results suggest the deficiency of recruitment of new B cells may unstabilize the immune system.

In Section 4, we observe the effect of invasions of antigen. We consider two cases: invasions of antigen at a tolerant state and at an autoimmune state. If there is no recruitment of new B cells, injection at a tolerant state can change the state both to an autoimmune state and to the neutral state, while injection at a autoimmune state can change it only to the neutral state.

Transition to the neutral state can be prevented for positive m because positive m stabilize the system. We can expect that small m can explain the transition from a tolerant state to autoimmune state by repeated invasions of antigen.

Because of the simplicity of the models, transition from an autoimmune state to a tolerant state, as described in [4], is not explained by this model. However we can expect that the consideration of B models will be a guide to observation of more complicated models. The asymmetry of the model suggests transition from an autoimmune state to a tolerant state (recovery from autoimmunity) is more unlikely than the reverse transition (onset of autoimmunity).

2. B models and autoimmunity

First we introduce a B model developed in [1]. Let $B_i(t)$ be the population of B cell clone i $(i = 1, 2)$ at time t. The proliferation of B cells is determined by the amount of stimulation h in accordance to the activation function

$$f(h) = \frac{h}{h+\theta_1}\frac{\theta_2}{h+\theta_2}, \tag{1}$$

where positive constants θ_1 and θ_2 satisfy $\theta_1 \ll \theta_2$. The function $f(x)$ is increasing for $0 < h < \sqrt{\theta_1\theta_2}$ and decreasing for $h > \sqrt{\theta_1\theta_2}$. The activation attains the maximum at the intermediate stimulation $h = \sqrt{\theta_1\theta_2}$. Then the dynamics of B_i is described by the equation

$$\frac{dB_i}{dt} = m + B_i(pf(h_i) - d), \tag{2}$$

where m is a source term for new B cells from the bone marrow, p and d are the proliferation rate and the death rate of B cells, respectively.

If we consider a two-clone model, where B_1 reacts with B_2 and B_2 reacts with B_1, we have $h_1 = B_2$ and $h_2 = B_1$. Thus we have a two-clone B model

$$\begin{aligned} \frac{dB_1}{dt} &= m + B_1(pf(B_2) - d), \\ \frac{dB_2}{dt} &= m + B_2(pf(B_1) - d). \end{aligned} \tag{3}$$

The qualitative features of (3) are investigated also in [1]. For estimated parameter values, system (3) has five equilibria $Q_0(q_0, q_0)$, $Q_1(q_1, q_1)$, $Q_2(q_3, q_2)$, $Q_3(q_2, q_3)$, and $Q_4(q_4, q_4)$, where $q_0 < q_1 < q_4$ and $q_2 < q_3$. Three of them, Q_0, Q_1, and Q_4, lie

on the diagonal $B_1 = B_2$, and the others, Q_2 and Q_3, lie on points symmetric with respect to the diagonal. The equilibria Q_0, Q_2, and Q_3 are locally asymptotically stable, and the others are unstable. (See also Section 3.)

We now consider autoimmunity with a B model. Suppose B_1 is autoreactive clone and B_2 is anti-idiotype of B_1. Then B_1 reacts with self-antigen and B_2, and B_2 reacts with B_1. We assume that the self-antigen u is constant. The assumption can be due to the homeostasis. Autoimmune disease generally has a long period symptom, and the autoimmune reaction can be expected not to be large. Thus we assume u is small. Then the system becomes

$$\begin{aligned} \frac{dB_1}{dt} &= m + B_1(pf(B_2 + u) - d), \\ \frac{dB_2}{dt} &= m + B_2(pf(B_1) - d). \end{aligned} \tag{4}$$

If u is small and the other parameters are estimated values as in (3), (4) also has five equilibria P_0, P_1, P_2, P_3, and P_4, which correspond to Q_0, Q_1, Q_2, Q_3 and Q_4, respectively. We can then show that P_2 and P_3 are locally asymptotically stable similarly to [1]. For the parameter values near that used in [1] and small u, we can show that P_0 is locally asymptotically stable and P_1 and P_4 are unstable.

According to [4], we call P_0 a neutral steady state, P_2 an autoimmune steady state, and P_3 a tolerant steady state. At the autoimmune steady state, autoreactive B cells (B_1) are susceptible to stimulation, and have large population in contrast to its anti-idiotype.

3. Qualitative analysis of models

In this section, we explore the global behavior of the solution of (4). We here assume that $m = 0$. The assumption meas that there is no recruitment of new B cells. This may be an ideal case, but it is a base for the consideration for the case $m > 0$.

We here deal with a general form of f including the function (1). Let $\alpha > 0$ be a constant and $f(x)$ be a continuously differentiable function on $[0, \infty)$ satisfying the following conditions:

1. $f(0) = 0$,
2. $f'(x) > 0$ for $0 < x < \alpha$,
3. $f'(x) < 0$ for $\alpha < x$,
4. $\lim_{x\to\infty} f(x) = 0$.

We put $M = f(\alpha)$, and fix positive constants d and p such that $0 < d < pM$. Then there exist two constants β_i $(i = 1, 2)$ such that $f(\beta_i) = d/p$ and $0 < \beta_1 < \alpha < \beta_2$.

Let u be a nonnegative constant such that $u < \beta_1$. We consider the following model whose variables are B_1 and B_2:

$$\begin{cases} \dfrac{dB_1}{dt} &= B_1(pf(B_2 + u) - d) \\ \dfrac{dB_2}{dt} &= B_2(pf(B_1) - d). \end{cases} \tag{5}$$

We investigate the qualitative properties for this model in the two case $u = 0$ and $u > 0$ separately. This model has the following five equilibria:

$$P_0(0,0), \quad P_1(\beta_1, \beta_1 - u), \quad P_2(\beta_2, \beta_1 - u), \quad P_3(\beta_1, \beta_2 - u), \quad P_4(\beta_2, \beta_2 - u).$$

The equilibrium $P_0(0,0)$ is clearly asymptotically stable. We calculate the Jacobi matrix in general form:

$$\begin{pmatrix} pf(B_2+u) - d & pB_1 f'(B_2+u) \\ pB_2 f'(B_1) & pf(B_1) - d \end{pmatrix} \tag{6}$$

The diagonal elements are zero at P_1, P_2, P_3 and P_4. Considering the signature of $f'(\beta_i)$'s, we conclude that P_2 and P_3 are neutrally stable and that P_1 and P_4 are saddle points. Vectors tangential at P_1 to the stable manifold have elements of opposite sign and vectors tangential at P_1 to the unstable manifold have elements of same sign. Vectors tangential at P_4 to the stable manifold have elements of same sign and vectors tangential at P_4 to the unstable manifold have elements of opposite sign.

We show that this model has a conservation quantity. We define a two variable function $G(B_1, B_2)$ by

$$G(B_1, B_2) = \int_{\beta_1}^{B_1} \frac{pf(\xi_1) - d}{\xi_1}\, d\xi_1 - \int_{\beta_1 - u}^{B_2} \frac{pf(\xi_2 + u) - d}{\xi_2}\, d\xi_2. \tag{7}$$

Proposition 1. *$G(B_1, B_2)$ is a conservation quantity for the system* (5).

Proof. When (B_1, B_2) moves along the differential equation (5), we have

$$\begin{aligned} \frac{dG}{dt} &= \frac{(pf(B_1) - d)}{B_1}\frac{dB_1}{dt} - \frac{(pf(B_2+u) - d)}{B_2}\frac{dB_2}{dt} \\ &= \frac{(pf(B_1) - d)}{B_1} B_1 (pf(B_2+u) - d) - \frac{(pf(B_2+u) - d)}{B_2} B_2 (pf(B_1) - d) \\ &= 0. \end{aligned}$$

□

This propositon shows that trajectories of the model lie in the curves $G(B_1, B_2) = C$ where C's are constants.

We investigate the values of $G(B_1, B_2)$. We calculate partial derivatives of $G(B_1, B_2)$ as follows:

$$\frac{\partial G}{\partial B_1} = \frac{pf(B_1) - d}{B_1}, \quad \frac{\partial G}{\partial B_2} = -\frac{pf(B_2+u) - d}{B_2}.$$

Then we have that $\partial G/\partial B_1$ is positive if $\beta_1 < B_1 < \beta_2$, is negative if $B_1 > \beta_2$ or $B_1 < \beta_1$, and is zero if $B_1 = \beta_1, \beta_2$, and that $\partial G/\partial B_2$ is negative if $\beta_1 - u < B_2 < \beta_2 - u$, is positive $B_2 > \beta_2 - u$, $B_2 < \beta_1 - u$ and is zero if $B_2 = \beta_1 - u, \beta_2 - u$.

In the region $(\beta_1, \infty) \times (0, \beta_2 - u)$, $G(B_1, B_2)$ is monotonically decreasing along any radial direction from the equilibrium point $P_2(\beta_2, \beta_1 - u)$, and in the region

$(0, \beta_2)\times(\beta_1-u, \infty)$, $G(B_1, B_2)$ is monotonically increasing along any radial direction from the equilibrium point $P_3(\beta_1, \beta_2 - u)$.

Let L be a positive constant such that $pf(x) \le d/2$ for $x \ge L$. Then for $B_1 \ge L$, we have

$$\begin{aligned} G(B_1, B_2) &\le \int_{\beta_1}^{L} \frac{pf(\xi) - d}{\xi}\, d\xi - \frac{d}{2}\int_{L}^{B_1} \frac{d\xi}{\xi} - \int_{\beta_1-u}^{B_2} \frac{pf(\xi+u) - d}{\xi}\, d\xi \\ &= -\frac{d}{2}\log\left(\frac{B_1}{L}\right) + \int_{\beta_1}^{L} \frac{pf(\xi) - d}{\xi}\, d\xi - \int_{\beta_1-u}^{B_2} \frac{pf(\xi+u) - d}{\xi}\, d\xi. \end{aligned}$$

From this, for a fixed $B_2 > 0$ we have

$$\lim_{B_1\to\infty} G(B_1, B_2) = -\infty.$$

Similarly, for a fixed $B_1 > 0$ we have

$$\lim_{B_2\to\infty} G(B_1, B_2) = \infty,$$

for a fixed $B_2 > 0$ we have

$$\lim_{B_1\to+0} G(B_1, B_2) = -\infty,$$

and for a fixed $B_1 > 0$ we have

$$\lim_{B_2\to+0} G(B_1, B_2) = \infty.$$

When (B_1, B_2) approaches the origin, $G(B_1, B_2)$ can tend to any real number as $t \to \infty$.

We determine the phase portrait of this system in two cases separately. We note that in both cases, clearly, there exists a heteroclinic orbit from P_1 to P_0.

3.1. The case $u = 0$

We consider the existence of heteroclinic orbits and homoclinic orbits.

PROPOSITION 2. *There exists a heteroclinic orbit from P_1 to P_4. This heteroclinic orbit is a line segment $\{(B_1, B_2) \mid B_1 = B_2,\ \beta_1 < B_1 < \beta_2\}$ as a curve.*

Proof. Since $u = 0$, the set $\{(B_1, B_2) \mid G(B_1, B_2) = 0\}$ in $(\beta_1, \beta_2)\times(\beta_1, \beta_2)$ is exactly equal to $\{(B_1, B_2) \mid B_1 = B_2\}$ in the region. Since vectors tangential at P_1 to the unstable manifold have elements of same sign, the desired heteroclinic orbits exists. □

We investigate the behavior of the solution extending the unstable manifolds of P_4, and show the existence of other heteroclinic orbits.

PROPOSITION 3. *There exists a heteroclinic orbit from P_4 to P_1 which lies at the right side of P_2. Similarly, there exists a heteroclinic orbit from P_4 to P_1 which lies at the left side of P_3.*

Proof. We take a point (B_1^0, B_2^0) on the unstable manifold of P_4 in the rectangle $(\beta_2, \infty) \times (\beta_1, \beta_2)$. The solution $(B_1(t), B_2(t))$ with initial point (B_1^0, B_2^0) moves in lower right direction, and moves lower left direction, and moves in upper left direction as t increase from 0. Finally, one of the following happens: it reaches the line segment $\{(\beta_1, B_2) \mid 0 < B_2 < \beta_1 - u\}$, or reaches the line segment $\{(B_1, \beta_1 - u) \mid \beta_1 < B_1 < \beta_2\}$ or tends to P_1 as $t \to \infty$. The value of $G(B_1, B_2)$ on the line segment $\{(\beta_1, B_2) \mid 0 < B_2 \leq \beta_1 - u\}$ is monotonically increasing as B_2 increase, that on the line segment $\{(B_1, \beta_1 - u) \mid \beta_1 \leq B_1 \leq \beta_2\}$ is also monotonically increasing and the value of $G(B_1, B_2)$ at P_1 is the same as that of P_4 by Proposition 2. Then the above solution must tend to P_1 as $t \to \infty$. Another case is similar. □

As for closed trajectories, the following holds.

Proposition 4. *In the regions surrounded by heteroclinic orbits, each solution is a closed trajectory surrounding one equilibrium if it does not coincide with the equilibrium. There exists no closed trajectory outside the regions.*

3.2. The case $u > 0$

When $u > 0$, the heteroclinic orbits in the case of $u = 0$ disappear, and homoclinic orbits appear.

Proposition 5. *Let $u > 0$. Then there exists a homoclinic orbit from P_1 to P_1 surrounding P_2, and a homoclinic orbit from P_4 to P_4 surrounding P_3. The solution moves clockwise on the first orbit, and moves anticlockwise on the second orbit.*

Proof. Since the vectors tangential at P_1 to the unstable manifold have elements of same sign, we can take a point (B_1^1, B_2^1) on the unstable manifold in the region $(\beta_1, \beta_2) \times (\beta_1 - u, \beta_2 - u)$. The solution with initial point (B_1^1, B_2^1) moves in upper right direction while it stays in the region $(\beta_1, \beta_2) \times (\beta_1 - u, \beta_2 - u)$. The value of $G(B_1, B_2)$ on the line segment $\{(\beta_2, B_2) \mid \beta_1 - u \leq B_2 \leq \beta_2 - u\}$ is monotonically decreasing as B_2 increases and that on the line segment $\{(B_1, \beta_2 - u) \mid \beta_1 \leq B_1 \leq \beta_2\}$ is monotonically decreasing as B_1 decreases. Since

$$\begin{aligned}
&G(\beta_2, \beta_2 - u) - G(\beta_1, \beta_1 - u) \\
&= \int_{\beta_1}^{\beta_2} \frac{pf(\xi) - d}{\xi}\, d\xi - \int_{\beta_1 - u}^{\beta_2 - u} \frac{pf(\xi + u) - d}{\xi}\, d\xi \\
&= \int_{\beta_1}^{\beta_2} (pf(\xi) - d)\left(\frac{1}{\xi} - \frac{1}{\xi - u}\right) d\xi \\
&< 0,
\end{aligned}$$

the solution reaches the line segment $\{(\beta_2, B_2) \mid \beta_1 - u < B_2 < \beta_2 - u\}$. After that the solution moves in lower right direction, and moves in lower left direction. As in the proof of Proposition 3, the solution must tend to P_1 as $t \to \infty$. Another case is similar. □

The system has another heteroclinic orbit.

PROPOSITION 6. *There exists a heteroclinic orbit from P_4 to P_0 lies in the right side of the homoclinic orbit surrounding P_2.*

Proof. We take a point (B_1^2, B_2^2) on the unstable manifold of P_4 in the region $(\beta_2, \infty) \times (\beta_1 - u, \beta_2 - u)$. It is clear that the solution with initial point (B_1^2, B_2^2) tends to P_0 as $t \to \infty$.

As for closed trajectories, the following holds.

PROPOSITION 7. *In the regions surrounded by homoclinic orbits, each solution is a closed trajectory surrounding one equilibrium if it does not coincide with the equilibrium. There exists no closed trajectory outside the regions.*

NOTE 3.1. There exists a backward orbit extending stable manifold of P_1 in upper left direction and a backward orbit extending stable manifold of P_4 in upper right directions. They separate the behaviour of the solutions drastically.

NOTE 3.2. The model which we consider in this section has a conservative quantity. But if the system has a source, the property of the system changes. Let m be a sufficiently small positive number. We consider the following model:

$$\begin{cases} \dfrac{dB_1}{dt} &= m + B_1(pf(B_2 + u) - d) \\ \dfrac{dB_2}{dt} &= m + B_2(pf(B_1) - d). \end{cases} \tag{8}$$

Put $\psi(B_1, B_2) = 1/(B_1 B_2)$. Then

$$\begin{aligned} &\frac{\partial}{\partial B_1}\{\psi \cdot (m + B_1(pf(B_2 + u) - d))\} + \frac{\partial}{\partial B_2}\{\psi \cdot (m + B_2(pf(B_1) - d))\} \\ &= -\frac{m(B_1 + B_2)}{B_1^2 B_2^2} < 0. \end{aligned}$$

This shows that the system has a Durac function. There exists no closed curves and homoclinic curves in the phase space of the above model.

4. Effect of invasions of antigen

In this section, we consider effect of additional antigen using the results in Section 3. First we assume $m = 0$, then the autoimmune and tolerant steady states, P_2 and P_3, are not asymptotically stable. However, inside the homoclinic orbits, all orbits are periodic. Hence we say the state is autoimmune when the orbit lies inside the homoclinic orbit which has the autoimmune steady state inside. The tolerant state can be defined similarly.

We will consider whether the invasion of antigen changes the state from one to another. We denote the density of the antigen by V. We introduce a model incorporating the invations of antigen. The antigen stimulates B_1 with the same

affinity as B_2 and u, and it decays proportionally to B_1 with rate k. We here consider the situation where the source m of B cells is equal to 0. It may be an ideal situation, but it is useful to see how the state can be changed. We thus have the equations, which is a B model version of the system in [4],

$$\begin{aligned} \frac{dB_1}{dt} &= B_1(pf(B_2+u+V)-d), \\ \frac{dB_2}{dt} &= B_2(pf(B_1)-d), \\ \frac{dV}{dt} &= -kB_1V. \end{aligned} \tag{9}$$

Because V decays to 0 as $t \to \infty$, the solution of (9) approaches the closed orbit defined by (5) as $t \to \infty$.

Assume that there is no additional antigen in the body, i.e. $V = 0$. Then B_1 and B_2 are governed by (5). The injection of antigen changes the orbit. After the injection at $t = t_0$, B_1, B_2, and V are changed according to (9). We consider how the injection affect the dynamics. For this purpose, we choose a closed orbit of model (5), which describes the dynamics without V, and take a point (B_1^0, B_2^0) on the orbit. Then we compare the orbit of (9) with initial condition

$$B_1(t_0) = B_1^0, \quad B_2(t_0) = B_2^0, \quad V(t_0) = V^0$$

to the original one.

Since we here deal with numerical computation, we must define the function form of f and determine the parameter values. We use the function (1) and the parameter values

$$p = 1.0, \quad d = 0.5, \quad \theta_1 = 10, \quad \theta_2 = 100, \quad u = 3.0, \quad k = 0.01.$$

These values are those estimated in [1] except u, k, θ_1, and θ_2. We use the values θ_1, θ_2 in [4] for better display of graphs of orbits. Since Sulzer and van Hammen [4] uses a different form of the function f and the roots β_1 and β_2 are about twice bigger than ours, we change the value u from 7 to 3. Then we have numerical values

$$\beta_1 = 13.0, \quad \alpha = 31.7, \quad \beta_2 = 77.0,$$

where $pf(h) - d > 0$ if $\beta_1 < h < \beta_2$ and $f(h)$ takes the maximum at $h = \alpha$. Note that from the previous discussion, we can see the change of values does not affect the qualitative behavior of the solutions.

Before considering the effect of the injection, we review a global figure of the phase space for (5) with $u > 0$ (Fig. 1). The system has two homoclinic orbits. One connects P_1 to itself. On the orbit, (B_1, B_2) moves clockwise. The other connects P_4 to itself. On it, (B_1, B_2) moves counter-clockwise. Inside these homoclinic orbits, the solutions of (5) form periodic orbits as mentioned in Section 3. Note

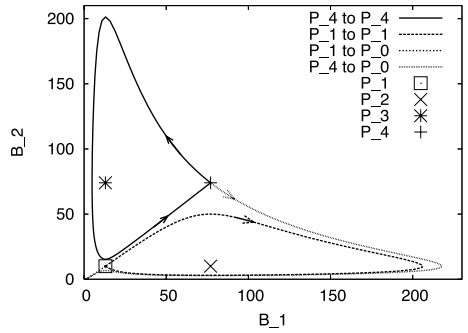

Fig. 1. The global behavior of the solutions of (5) when $u \neq 0$.

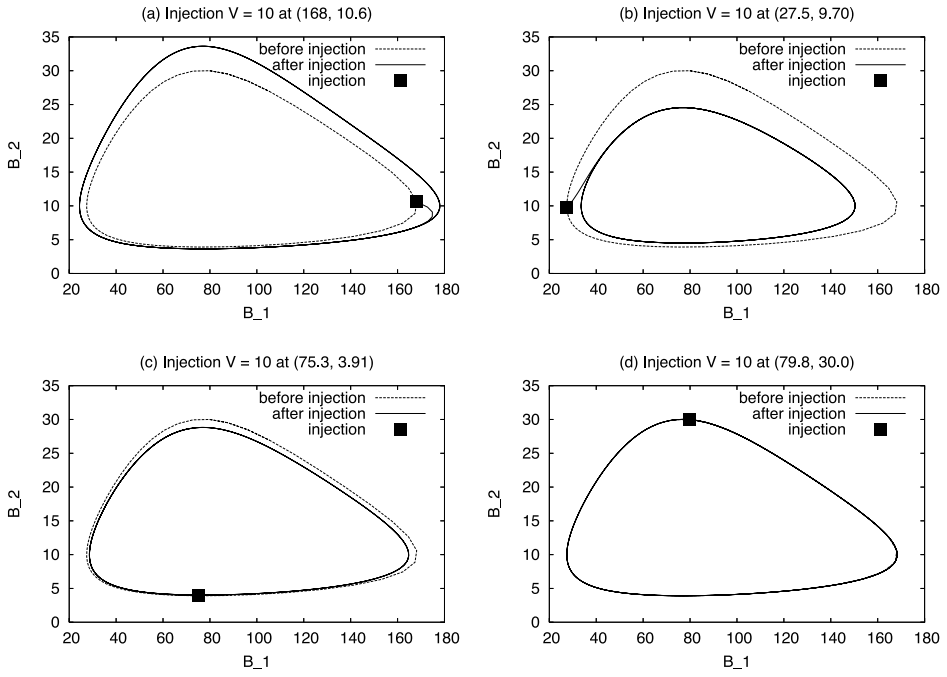

Fig. 2. The effect of injection for the autoimmune state.

that the shift between the tolerance and autoimmune states occurs when the orbit moves across one of the homoclinic orbits.

First we consider the case where a closed orbit of model (5) lies inside the homoclinic orbit in the region $\{(B_1, B_2) \in \operatorname{Int} \mathbf{R}^2_+;\ B_1 > B_2 - u\}$. This case corresponds to the autoimmune state. Fig. 2 shows the shift of orbits by the injection of antigen at (B_1^0, B_2^0).

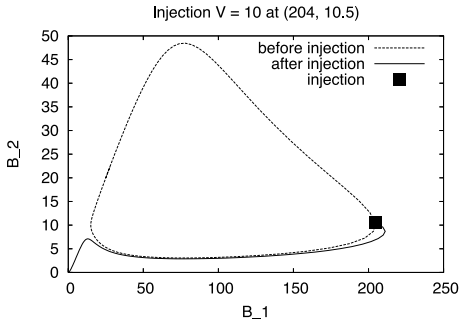

Fig. 3. The orbit tends to $(0, 0)$ after the injection

The injection affects the orbit in accordance with the value B_2 at the injection. The injection at (B_1^0, B_2^0) with B_2^0 near 10 implies the increase of B_1 (Fig. 2 (a), (b)). The increase results in increase of amplitude when (B_1^0, B_2^0) lies on right side of the orbit (Fig. 2 (a)) and in decrease of amplitude when it lies on the left side (Fig. 2 (b)). Fig. 2 (c) shows injection does not immediately affect the orbit because the change of B_1, keeping B_2 unchanged, affects the orbit little, but after that the remaining antigen affects the orbit like in the case (b). Note that $(B_1(t), B_2(t))$ moves clockwise on this orbit. Fig. 2 (d) shows that the injection does not affects the orbit.

The change of state occurs only when the orbit is enlarged by the injection. The change actually occurs when the amplitude of the orbit is large and the antigen is injected when (B_1, B_2) is on the right side of the orbit (Fig. 3). But the state changes to the neutral state $(0, 0)$, not to a tolerant state. We can see from the observation above that it is unlikely that a state changes from an autoimmune state to a tolerance state.

Next we consider the transition from a tolerance state. Assume the orbit originally lies inside the homoclinic orbit in the region $\{(B_1, B_2) \in \operatorname{Int} \mathbf{R}_+^2; B_1 < B_2 - u\}$.

Fig. 4 shows the shift of orbit by the injection of the antigen. When $B_2 + u > \alpha$, the injection prevents B_1 from increasing. Since $u = 3$ and $\alpha \fallingdotseq 31.7$, the orbits shifts to left after the injection in Fig. 4 (a), (b), (c). Consequently the altered orbit lies inside the original one in case (a), and it lies outside the original in case (b) and (c).

The enlargement of the orbit by the injection is likely to occur in this case. The outside shift of the orbit can result in a transition from the tolerance state toward the autoimmune state (Fig. 5). The trajectory finally approaches to the neutral state $(0, 0)$.

We see that the state can move from a tolerant region to a autoimmune state and it remains in the autoimmune state approaching the closed orbit, when the antigen titer V^0 is large. Then the remaining antigen moves the orbit across the homoclinic orbit (Fig. 6).

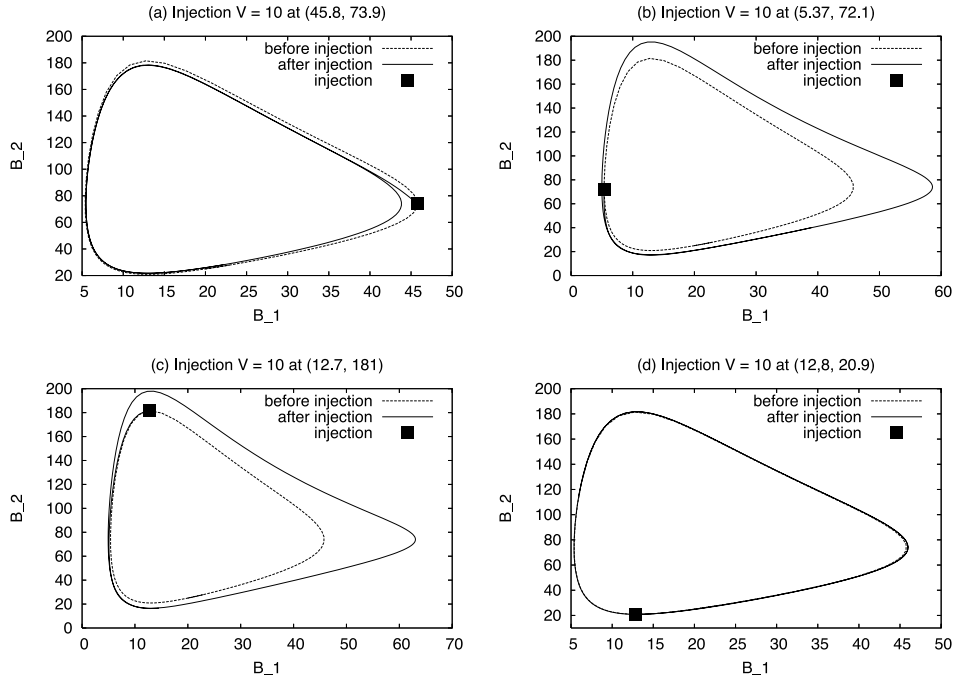

Fig. 4. The effect of injection for the tolerant state.

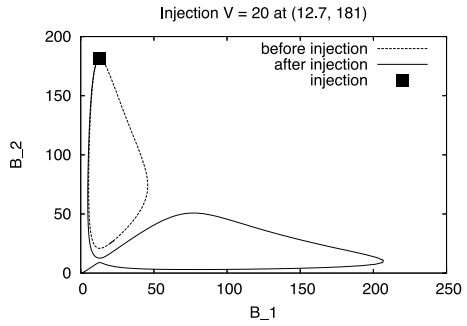

Fig. 5. The shifted orbit first runs near the autoimmune orbit and finally approaches $(0, 0)$.

Next we consider the case $m > 0$. Then we have equations

$$\begin{aligned} \frac{dB_1}{dt} &= m + B_1(pf(B_2 + u + V) - d), \\ \frac{dB_2}{dt} &= m + B_2(pf(B_1) - d), \\ \frac{dV}{dt} &= -kB_1V. \end{aligned} \tag{10}$$

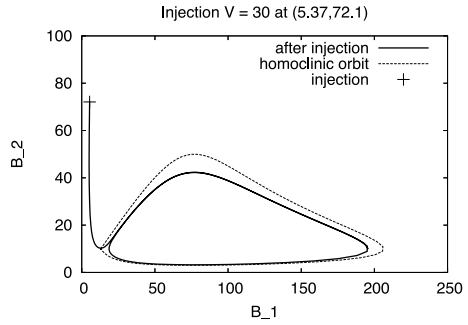

Fig. 6. The orbit shifts to the autoimmune state.

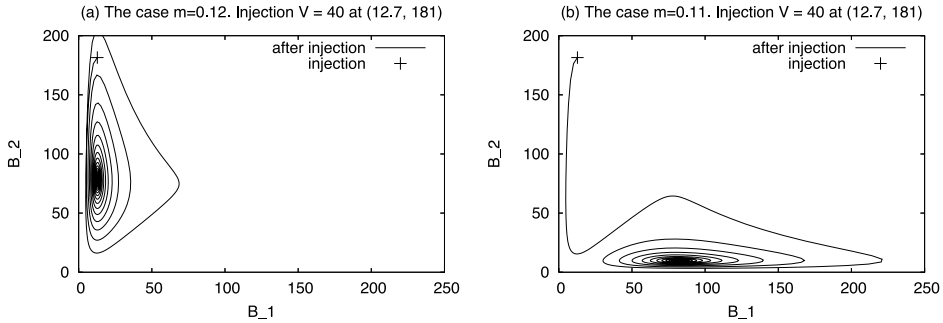

Fig. 7. The effect of the injection for nonzero m.

In this case, the orbit can be attracted to the equilibria P_2 or P_3. Fig. 7 (a) shows, if m is not small, the orbit is attracted to P_3 and the transition is prevented. Conversely if m is small, the orbit can be attracted to P_2 after the transition from the tolerance domain to the autoimmune domain (Fig. 7 (b)).

5. Discussion

In our model, the lack of birth of new B cells ($m = 0$) makes the system structurally unstable. Small perturbations, such as the invasion of the antigen, can change the orbit of the solution. After the perturbation, the solution changes periodically along a closed orbit. Because the effect of a perturbation remains forever, repeated perturbations can move the orbit extensively and can result in the transition of states. Hence this model suggests that the immune system becomes unstable when $m = 0$.

If $m = 0$, the trajectory is likely to approaches to $(0, 0)$ after the transition. It means that the autoimmunity vanishes. The case $m = 0$ may correspond to the case where few kinds of epitopes are involved and the source of the B cells is deficient.

The positive value of m, for example, may keep the orbit from approaching to $(0, 0)$ after the transition. Fig. 7 shows that the orbit after the injection can

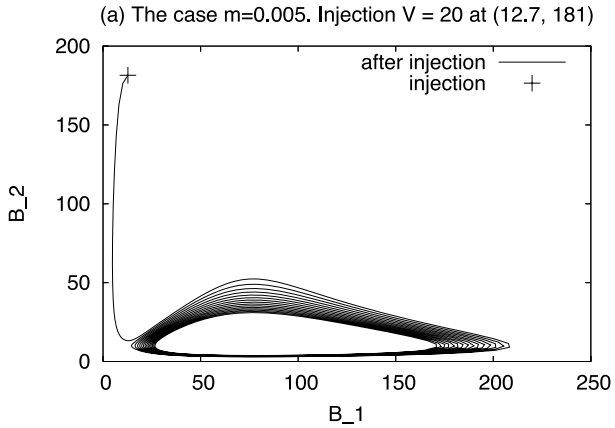

Fig. 8. The orbit shifts from the sink of P_2 to that of P_3 by the injection.

approach both the tolerant and autoimmune steady states. If m is small, the attraction to P_3 is then so weak that the effect of a perturbation remains long. Repeated perturbations therefore can shift the orbit from near P_3 to the sink of P_2. Fig. 8 shows the transition by the injection from the sink of P_3 to that of P_2. We can see that the attraction to P_2 is very small and the trajectory approaches to P_2 very slowly. This may express an onset of an autoimmune disease. Small m may correspond to the case where many kinds of epitopes are involved and the source of B cells is deficient. The results also show that the autoimmune disease might be hard to recover from in this case.

The asymmetry of the model makes the difference of probability between the transition from a tolerance state to an autoimmune state and the inverse transition. The discussions in Sections 3 and 4 show that the flow has a tendency to move from the region $\{(B_1, B_2) \mid B_1 < B_2 - u\}$ to $\{(B_1, B_2) \mid B_2 - u < B_1\}$. (See also Fig. 1.) This suggests difficulty of treatment of autoimmune diseases.

Sulzer and van Hemmen [4] suggest that the controlled dose can shift the state from an autoimmune state to a tolerant state. But our model does not explain such a transition. The difference may come form a simplicity of our model. Our model is essentially two dimensional (B_1 and B_2), and the trajectory is restricted in the low dimensions. It may be a reason why our model cannot explain the shift from the autoimmune state to the tolerant state but to $(0, 0)$. We note that the effect of the injection of antigen in the autoimmune state is large when B_1 is large in our model. This suggests the controlled dose of antigen according to the auto-antibody titer in [4] is effective.

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