

## IMMUNE SYSTEM MEMORY REALIZATION IN A POPULATION MODEL

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**ABSTRACT.** A general process of the immune system consists of effector stage and memory stage. Current theoretical studies of the immune system often focus on the memory stage and pay less attention on the function of non-immune system substances such as tissue cells in adjusting the dynamical behavior of the immune system. We propose a mathematical population model to investigate the interaction between influenza A virus (IAV) susceptible tissue cells and generic immune cells when the tissue is invaded by IAV. We carry out a linear stability analysis and numerically study the Neimark-Sacker bifurcation of the models. The behavior of the model system agrees with some important experimental or clinical observations for IAV. However, we show that without considering the space between tissue cells, the expected memory stage does not form. By considering the space which allows antibodies to bind antigens, the memory stage then forms without missing the property of the system in the effector stage.

**1. Introduction.** A general immune process includes “effector stage” and “memory stage” (Ahmed & Gray, 1996; Antia *et al.*, 1998; Badovinac & Harty, 2003). In the effector stage, the population of antigen-specific immune cells first increases rapidly due to the stimulation of the antigen and then decreases quickly because of the lack of the stimulation—most antigens have been killed—and the limit turnover of the most immune cells. The population of the immune cells will not decrease to zero but stop decreasing and maintain at a certain level. The system then is in the memory stage. One of the important and open questions in the study of the immune system is how the system builds memory and maintains the immune repertoire. The current theoretical study of the immune system focuses on the interaction among the different kinds of immune cells while the function of antigens on the immune system is often taken as either a simple form or an independent form (McLean, 1992; Wodarz *et al.*, 2001a; Antia *et al.*, 1998, 2003). This methodology can simplify modelling equations and obtain some most important properties of the immune system, for example, it has been known that the immune system has equilibrium, periodic and even more complicated behavior. However, it is not fully known whether and how these states can be connected in a whole immune process. The work of Wodarz (2001b) and Antia *et al.* (1996) shows that when the immunological pressure due to cytotoxic T-lymphocytes (CTLs) is strong, the virus

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can be cleared and the memory stage can be formed, and otherwise the virus can attain a high density. Their simple models are logically robust, but because the immune system is highly nonlinear and the function of antigens on the system can be very complicated, it is useful to check the case in which tissue cells and viruses are invited into immune response models. One of the advantages of such a “bigger” system is that we can validate the model with clinical observations because many observations are based on tissue cells. More importantly we may use the model to explore, for instance, how the interaction between pathogens and tissue cells affect the form of the memory stage in a more natural way.

Motivated by these considerations, in this work, we investigate how the dynamical behavior of the immune system is effected by the more complicated form of the function of the antigen, and particularly how the immune system optimally adjusts itself to realize the memory stage. To achieve this, we build a population model by utilizing the basic ideas in a cellular automata(CA) model in Beauchemin *et al.* (2004) and focus on the immune response in our model. The reason for us to adopt this CA model is that the results from this simple model agree with clinical observations well for influenza A virus(IAV). In order to understand how the immune system optimizes the immune process, we study the equilibria and their stability of our model. It turns out that the system is periodic in the chosen parameter region. This indicates that the virus-free equilibrium is unstable and the system is in a repeated infection process, and thus the memory stage is not built up.

We show that there is a virus-persistent equilibrium between the virus-free equilibrium and the periodic state, and that the virus-free and virus-persistent equilibria are stable in some parameter region, and that the periodic and equilibria states can be combined together by letting the infection rate of virus and cells be a monotonic function because of antibodies. The general immune process is then realized in our model and the mechanism of the switch between the effector stage and memory stage is explained to some extent.

**2. The model.** Our model is built on the recently developed CA model in Beauchemin *et al.* (2004), and the basic ideas of the CA model are described below.

The CA model considers two kinds of cells: epithelial cells and immune cells. The epithelial cells are fixed in a two-dimensional lattice map with each cell per lattice, and the immune cells randomly walk on the map. An epithelial cell can be in one of five states: healthy, infected, expressing, infectious and dead, while an immune cell is in one of three states: virgin, mature and dead. The virus particles are not explicitly considered in the model, though it is assumed that the infection can spread from one epithelial cell to its neighbors. The healthy cell may become infected if some of its nearest neighbors are infectious; the infected cell will develop itself into an expressing state after some time(delay), and further into an infectious state. When the cell is infectious, it can infect its healthy neighbors. The virgin immune cell becomes mature once it encounters an expressing or infectious cell, and the mature cell causes an encountered expressing or infectious cell to be dead and meanwhile reproduces itself with some delay. The mature cells biologically correspond to the antigen-specific immune cells but do not include the memory cells. All the cells have ages and will die when they reach their lifespan. A dead epithelial cell will be revived at some rate. All the number of cells can change with time except the number of virgin immune cells that maintains a minimum density.

The values of parameters are mostly adopted from Bocharov and Romanyukha (1994) and listed in Table 1.

Since we are interested in the immune process, we must incorporate memory cells into our model formulation explicitly. For this purpose, we note that in the real immune system, mature immune cells may transform into memory immune cells if the mature cells have not been stimulated for some time (Perelson & Weisbuch, 1997; Bocharov & Romanyukha, 1994; Clough & Roth, 1998), or some memory cells may be generated during the effector stage with or without the common precursors as the mature immune cells (Clough & Roth 1998; Dooms & Abbas, 2002). The memory cells have longer lifespan than the mature cells and may be more active than the virgin immune cells (Gray, 2000; Veiga-Fernandez *et al.*, 2000; Rocha, 2002) although it is not fully understood how many of the mature cells will transform into the memory cells (Clough & Roth, 1998) (if we consider the transformation case) and how long the lifespan of the memory cells is (Borghans *et al.*, 1999). In the literature, it is estimated that 5%-10% mature cells will divide into memory cells (Kaech *et al.*, 2003) and the lifespan of the memory cells can be from several days to years (Clough & Roth, 1998). Memory cells normally are in inactivated state unless stimulated, and activated memory cells may have a similar effectiveness as matured immune cells in killing virus. Thus, for simplicity, here we assume that (i) memory cells are differentiated from mature cells, (ii) the total number of memory cells differentiated from mature cells during the effector stage is about 10% of the maximum number of the mature cells, (iii) as a whole, the effectiveness of memory cells (inactivated and activated) in killing virus and infectious cells is less than the effectiveness of mature cells, and (iv) the lifespan of memory cells is long enough in our investigation period, that is, the number of memory cells increases as the number of mature cells increases but does not decrease when the number of mature cells decreases.

Next, we translate the CA model into a population or probability mathematical model so that we can analyze the immune response mathematically. For convenience, we consider the homogeneous case. The diagram of the population transform between different states (except the memory state, see later) of cells is depicted in Fig. 1 and the values of parameters are listed in Table 1. Because cells have limited lifespan and some transformation between states needs time, it is natural to formulate an age-dependent population model.

The evolution of healthy epithelial cells from time  $t$  to  $t + 1$  is

$$\begin{aligned}
 H(t + 1, 0) &= \tau_{div}^{-1} D(t), \\
 H(t + 1, i) &= \left(1 - \frac{\gamma_{inf}}{N} PI2(t)\right) H(t, i - 1), \quad i = 1, 2, \dots, \tau_h, \\
 PH(t + 1) &= \sum_{i=0}^{\tau_h} H(t + 1, i) \\
 &= \left(1 - \frac{\gamma_{inf}}{N} PI2(t)\right) (PH(t) - H(t, \tau_h)) + H(t + 1, 0),
 \end{aligned} \tag{1}$$

where  $H(t, i)$  is the number of healthy epithelial cells at time  $t$  and age  $i$ ,  $D(t)$  the number of dead epithelial cells at  $t$ ,  $PI2(t)$  and  $PH(t)$  are respectively the population of infectious and healthy epithelial cells at  $t$ , and  $N$  the total number of epithelial cells (including dead epithelial cells). Because a cell's age,  $\tau_h$ , is usually much less than the lifespan of the host, we may treat  $N$  as a constant during the immune process. Healthy new born cells (at age 0) come from the division of the healthy cells. When  $N$  is a constant, the division happens only when there are one

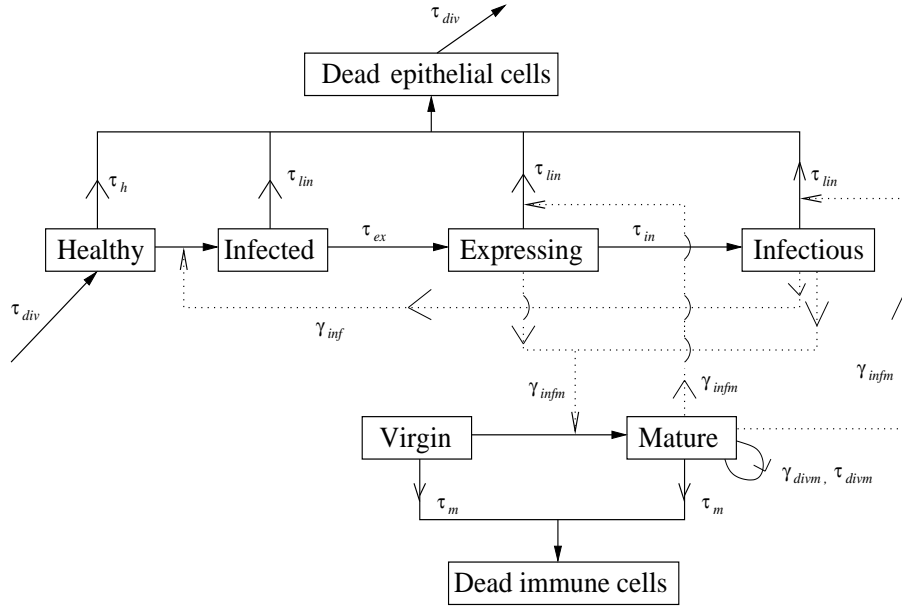


FIGURE 1. Block diagram of the population transform in our model.

or more dead cells. Further we assume that the number of healthy cells will not be zero so that when dead cells exist there are always some healthy cells ready to divide. In this case, we may say that if there is no dead cell, no new cell will be born, and the more cells die, the more new cells will be born. Thus, we simply assume that at  $t+1$  the number of new born cells,  $H(t+1, 0)$ , is directly proportional to the number of dead cells at  $t$ . However, we note that in this case the division time,  $\tau_{div}$ , should be larger than the real cell's division time, especially for our homogeneous population model. This is because the healthy cells in a tissue may divide when the nearest cell is dead; when most cells are died in a specific part of the tissue, which often happens in IAV infection, it may take several division times for these dead cells to be replaced by new healthy cells, but our homogeneous assumption treats the healthy and dead cells uniformly mixed; therefore, if the number of healthy cells is greater than the number of dead cells, in our model, these dead cells will be replaced during one division time. By taking this consideration into our model, we choose the value of  $\tau_{div}$  to be 30 hours which is somewhat greater than the upper bound of the real division time, 24 hours (Beauchemin *et al.* (2004)). For the infection rate  $\gamma_{inf}$  we assume it is the same for each component of healthy and infectious cells no matter what their age and amount are. More discussions will be given later.

The infected cells ( $I1$ ) are originally from the healthy epithelial cells that have different ages. Thus, each infected cell has both the *infected age* (starting from the time at which it was infected) and *natural age* (starting from the time at which it was born). For convenience, we consider those with the same infected age  $i$  at time  $t$  as a group expressed by  $I1(t, i)$ . For every  $i \in [0, \tau_{ex}]$ ,  $I1(t, i)$  has a distribution on the natural age, where  $\tau_{ex}$  is the typical time interval for the infected cells to become expressing. Because the lifespan of infected cells is less than the lifespan

TABLE 1. The parameters in our model for IAV

Parameter	Value	Description
$\tau_h$	$380h$	Lifespan of a healthy epithelial cell
$\gamma_{inf}$	$1.3h^{-1}$	Infection rate between healthy and infectious cells
$\tau_{ex}$	$4h$	Delay from infected to expressing
$\tau_{in}$	$2h$	Delay from expressing to infectious
$\tau_{lin}$	$24h$	Lifespan of an infected epithelial cell
$\tau_{div}$	$30h$	Duration of an epithelial cell division
$\tau_m$	$168h$	Lifespan of an immune cell
$\gamma_{infm}$	$6h^{-1}$	Encounter rate between mature immune and epithelial cells
$\gamma_{infmm}$	$0.6h^{-1}$	Encounter rate between memory immune and epithelial cells
$\tau_{divm}$	$7h$	Delay of a mature immune cell reproduction
$\gamma_{divm}$	$0.25h^{-1}$	Rate of a mature immune cell reproduction
$\gamma_m$	$1.5 \times 10^{-2}$	Minimum density of immune cells per epithelial cell

of healthy cells, we assume that originally healthy cells with age greater than  $\tau_{lin}$ , the lifespan of infected cells, are dead when they become infected. From  $t$  to  $t + 1$ , or equivalently from the infected age  $i - 1$  to  $i$ , those infected cells with natural age  $\tau_{lin} - i + 1$  will die, and the number of infected cells at infected age  $i$  will be proportional to  $\frac{\gamma_{inf}}{N} \sum_{j=0}^{\tau_{lin}-i} H(t, j)$ . Therefore, from  $t$  to  $t + 1$ , we have

$$I1(t + 1, i) = \frac{\frac{\gamma_{inf}}{N} \sum_{j=0}^{\tau_{lin}-i} H(t, j)}{\frac{\gamma_{inf}}{N} \sum_{j=0}^{\tau_{lin}-i+1} H(t, j)} I1(t, i - 1) = \frac{\sum_{j=0}^{\tau_{lin}-i} H(t, j)}{\sum_{j=0}^{\tau_{lin}-i+1} H(t, j)} I1(t, i - 1).$$

To simplify the expression above, here we assume that  $H$  is well distributed. (This assumption is reasonable at the beginning of infection because before the infection  $H$  is usually well distributed.) Thus

$$I1(t + 1, i) = \frac{\tau_{lin} - i + 1}{\tau_{lin} - i + 2} I1(t, i - 1) \quad i = 1, 2, \dots, \tau_{ex}.$$

Because for IAV,  $\tau_{ex} \ll \tau_{lin}$ , we may further simplify the expression above as

$$I1(t + 1, i) = \left(1 - \frac{1}{\tau_{lin}}\right) I1(t, i - 1), \quad i = 1, 2, \dots, \tau_{ex}.$$

Therefore, for the infected cells the evolution of their components from  $t$  to  $t + 1$  is expressed as

$$\begin{aligned} I1(t + 1, 0) &= \frac{\gamma_{inf}}{N} PI2(t)(PH(t) - H(t, \tau_h)), \\ I1(t + 1, i) &= \left(1 - \frac{1}{\tau_{lin}}\right) I1(t, i - 1) \quad i = 1, 2, \dots, \tau_{ex}, \\ PI1(t + 1) &= \sum_{i=0}^{\tau_{ex}} I1(t + 1, i) \\ &= \left(1 - \frac{1}{\tau_{lin}}\right) (PI1(t) - I1(t, \tau_{ex})) + I1(t + 1, 0). \end{aligned} \tag{2}$$

where  $PI1(t)$  is the population of infected cells at  $t$ . Similarly, when  $\tau_{lin} \gg \tau_{ex} + \tau_{in}$ , where  $\tau_{in}$  is the typical time interval for the expressing cells to become infectious, for the expressing cells ( $E$ ) and infectious cells ( $I2$ ) we may have

$$\begin{aligned} E(t+1, 0) &= (1 - \frac{1}{\tau_{lin}})I1(t, \tau_{ex}), \\ E(t+1, i) &= (1 - \frac{1}{\tau_{lin}})f(PM(t), PMM(t))E(t, i-1), \quad i = 1, 2, \dots, \tau_{in}, \\ PE(t+1) &= (1 - \frac{1}{\tau_{lin}})f(PM(t), PMM(t))(PE(t) - E(t, \tau_{in})) + E(t+1, 0), \end{aligned} \quad (3)$$

where  $f(PM, PMM) = 1 - \frac{\gamma_{infm}}{N}PM - \frac{\gamma_{infmm}}{N}PMM$  and  $PE(t)$ ,  $PM(t)$  and  $PMM(t)$  are respectively the population of infected cells, mature immune cells and memory immune cells at  $t$ ,  $\gamma_{infm}$  and  $\gamma_{infmm}$  are respectively the encounter rates of mature immune cells and memory immune cells with the expressing cells, and

$$\begin{aligned} I2(t+1, 0) &= (1 - \frac{1}{\tau_{lin}})f(PM(t), PMM(t))E(t, \tau_{in}), \\ I2(t+1, i) &= (1 - \frac{1}{\tau_{lin}})f(PM(t), PMM(t))I2(t, i-1), \quad i = 1, 2, \dots, \tau_{lin}, \\ PI2(t+1) &= (1 - \frac{1}{\tau_{lin}})f(PM(t), PMM(t))(PI2(t) - I2(t, \tau_{lin}) + E(t, \tau_{in})). \end{aligned} \quad (4)$$

The total number of dead epithelial cells ( $D$ ) at  $t+1$  is

$$D(t+1) = N - PH(t+1) - PI1(t+1) - PE(t+1) - PI2(t+1). \quad (5)$$

We further assume that the virgin immune cells can be supplied by, say, the bone marrow quickly so that the concentration of the virgin immune cells is maintained without change. Denote the number of virgin immune cells by  $V$ , the mature immune cells ( $M$ ) evolves from  $t$  to  $t+1$  as follows:

$$\begin{aligned} V &= \gamma_m N, \\ M(t+1, 0) &= \frac{\gamma_{divm}}{N}(PE(t) + PI2(t))V + \gamma_{divm}M(t - \tau_{divm}, 0), \\ M(t+1, i) &= M(t, i-1), \quad i = 1, 2, \dots, \tau_m, \\ PM(t+1) &= PM(t) - M(t, \tau_m) + M(t+1, 0). \end{aligned} \quad (6)$$

Here,  $\gamma_{divm}$  is the reproduction rate of (activated) mature immune cells and  $\tau_{divm}$  is the delay of the reproduction. The term  $\gamma_{divm}M(t - \tau_{divm}, 0)$  comes from the assumption that the mature immune cells reproduce only once. This assumption can be relaxed by replacing the term by, say,  $\gamma_{divm}PM(t - \tau_{divm})$  so that the cells can always reproduce during their life. For the single reproduction case, we found that the value of  $\gamma_m$  should be taken as the permitted upper bound,  $1.5 \times 10^{-2}$  (see later), while for the multiple reproduction case,  $\gamma_m$  should be at the lower bound,  $1.5 \times 10^{-4}$ , so that the results from our model agree with the experimental and clinical observations for IAV, but our main result keeps unchanged about the stability of virus-free equilibrium and the formation of memory stage.

For the total population of memory cells ( $PMM$ ), we have

$$PMM(t+1) = \begin{cases} 0.1PM(t) & \text{if } PM(t+1) > PM(t), \\ PMM(t) & \text{otherwise.} \end{cases} \quad (7)$$

The expression for the dead immune cells is omitted because under our assumptions, it will not affect the immune process.

The parameter values considered in our model are mostly adopted from (Bocharov & Romanyukha, 1994; Beauchemin *et al.* 2004). It is noted that the value of  $N$  does not affect the dynamical behavior of our model because it can be also explained as a probability model. Some explanations are given below on the determination of

parameter values,  $\gamma_{inf}$  and  $\gamma_m$ , which are somewhat different from those used in the CA model (Beauchemin *et al.* 2004):

- (1)  $\gamma_{inf}$  is used as a free parameter in our work, but the range of its value can be estimated. For IAV, with 1% initial infection rate, the fraction of dead epithelial cells reaches 40% on day 2 (Bocharov & Romanyukha, 1994). Therefore, we may have  $\gamma_{inf} = 40\%/1\%/(24 \sim 48) = 1.7 \sim 0.9h^{-1}$ .
- (2) The permitted range of reactive virgin immune cells per epithelial cell is  $\gamma_m = 1.5 \times 10^{-4} \sim 1.5 \times 10^{-2}$  estimated as follows. There are about 15 intraepithelial lymphocytes per 100 epithelial cells and the probability for an immune cell to recognize an epitope is about  $10^{-5}$  (Beauchemin *et al.*, 2004), and for IAV, the number of specific high-affinity receptors of IFN varies from  $10^2$  to  $10^4$  (Bocharov & Romanyukha, 1994), therefore, we may have  $\gamma_m = (15/100) \times 10^{-5} \times (10^2 \sim 10^4) = 1.5 \times 10^{-4} \sim 1.5 \times 10^{-2}$ .

To numerically simulate the system that consists of Eq. (1), we use the initial and boundary conditions as follows. The ages of healthy epithelial cells are uniformly distributed between 0 and  $\tau_h$  inclusive, and so are the ages of infected cells but between 0 and  $\tau_{in}$  inclusive. The number of infected cells is  $1\%N$ . The numerical simulations of our model are displayed in Figures 2(a) and 2(b).

One can see from Fig. 2 that when  $t \in [0, 200]$  hours, the system is in the effector stage. The numerical simulations at this stage agree following clinical observations for IAV. (1) The infection reaches its peak on day 2 (Bocharov & Romanyukha, 1994; Hayden *et al.*, 1998); (2) the fraction of dead epithelial cells is 10% on day 1, 40% on day 2 and 10% on day 5 (Bocharov & Romanyukha, 1994); (3) the virus concentration declines to inoculation level on day  $5 \pm 2$  (Bocharov & Romanyukha, 1994; Hayden *et al.*, 1998; Fritz *et al.*, 1999); (4) the concentration of immune cells achieves its maximum between day 2 and day 7, and the maximum is 10-fold and up to  $10^2$ -fold greater than the normal concentration (Bocharov & Romanyukha, 1994). This seems to provide a convincing validation for our model. However, when simulating our model into a long time, we find that the virus is not completely suppressed but will break out periodically as shown in Fig. 2(b).

Interestingly, in our numerical simulation, if we enforce a condition that if the number of infected cells,  $E(t, i)$ , is much less than 1, say  $10^{-16}$ , the number is set to be zero, then the periodic phenomenon no longer appears and the virus is completely suppressed. Such an observation might be reasonable for population models because the number of subjects is an integer, and might explain why the periodic motion does not exist in the CA model (Beauchemin *et al.*, 2004) where the number of cells is an integer. However, it cannot explain the essential function of the immune system because only if a small number of viruses ( $> 1$ ) invade the host during the memory stage, the whole immune process, namely the periodic process, will be triggered again. This phenomenon is obviously opposite to clinical and experimental findings, and actually the memory stage does not form although the population of memory cells,  $PMM$ , is not small. We emphasize that a similar problem also happens in other immune system models (Bocharov & Romanyukha, 1994) in which the parameter values are estimated from experiments. To solve the problem calls for more detailed quantitative analysis, provided in the following.

**3. The equilibria and their stability.** The equilibria of the system that consists of Eq. (1) – Eq. (7) can be determined in the following way. When letting the variables of the system change neither with time nor with age, for instance,  $H(t, i) =$

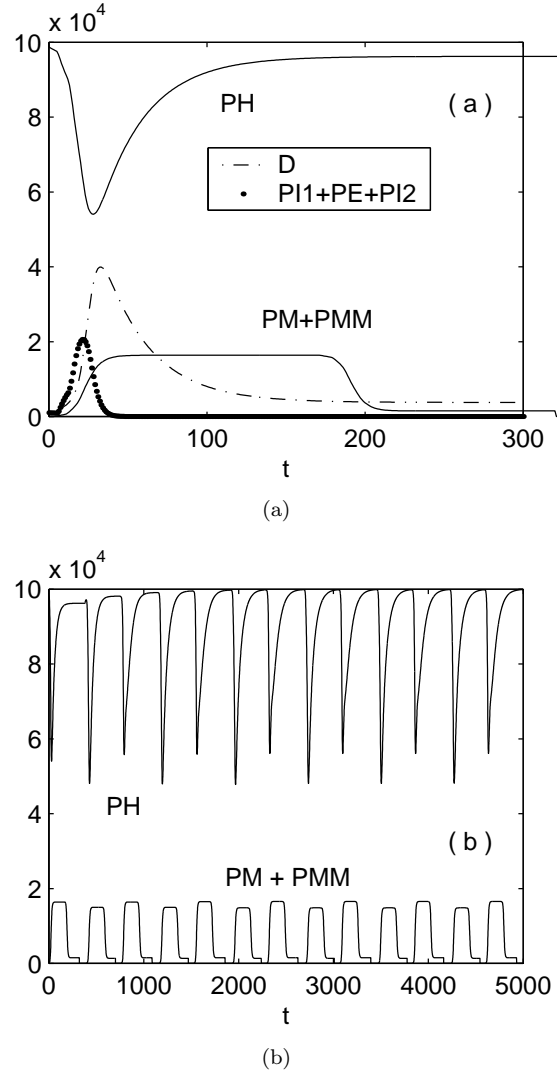


FIGURE 2. (a) The population evolution of healthy epithelial cells ( $PH$ ), virus-containing epithelial cells ( $PI1 + PE + PI2$ ), dead epithelial cells ( $D$ ) and immune cells ( $PM + PMM$ ) when  $t \in [0, 300]$  hours. (b) The periodic oscillation of the population of healthy epithelial cells and immune cells when  $t \in [0, 5000]$  hours.

$\hat{H}$ , where  $\hat{H}$  denotes the number of epithelial cells in the equilibrium state, we obtain the equilibrium

$$(P\hat{H}, P\hat{I}_1, P\hat{E}, P\hat{I}_2, \hat{D}, P\hat{M}, P\hat{M}M) = \left( \frac{(\tau_h + 1)N}{\tau_h + 1 + \tau_{div}}, 0, 0, 0, \frac{\tau_{div}N}{\tau_h + 1 + \tau_{div}}, 0, c \right),$$

which is called the virus-free equilibrium because all variables relative to the virus,  $P\hat{I}_1$ ,  $P\hat{E}$ ,  $P\hat{I}_2$ , are zero at the equilibrium. Here,  $c$  is the number of memory cells during the memory stage. And when the variables of the system do not change



with time but allowing the number of the repertoire (at different discrete ages) of each variable to be different, for example,  $H(t, i) = \hat{H}(i)$ , where  $\hat{H}(i)$  denotes the number of epithelial cells at age  $i$  in the equilibrium state, we can obtain the virus-persistent equilibrium where none of  $P\hat{I}1, P\hat{E}, P\hat{I}2$  is zero. The expression of the equilibrium is complicated, and is omitted.

We are interested in these two equilibria because they correspond to two types of memory states of the immune system: one is the ideal virus-free memory state and the other is virus-persistent memory state for which much experimental and theoretical work has been done (Kundig *et al.*, 1996a, 1996b, Wodarz *et al.*, 2000a, 2000b, 2001b) to investigate the role of CTLs. Also, from Fig. 2 we see that the system approaches the virus-free equilibrium after the effector stage, and a virus-persistent memory stage could be built around the virus-persistent equilibrium if this equilibrium is stable. We shall see that the general immune process can be realized in our system by switching the dynamical behavior of the system from the effector stage to one of these two equilibria.

The stability of the virus-free equilibrium can be rigorously analyzed. At this equilibrium,  $PMM(t) = c$  is a constant and the value of  $c$  may depend on all other parameter values of the system and the boundary condition. The linearized system of Eq. (1) – Eq. (6) at this equilibrium can be expressed as

$$\delta\mathbf{x}(t+1) = \begin{bmatrix} \mathbf{A} & \mathbf{0} \\ \mathbf{B} & \mathbf{C} \end{bmatrix} \delta\mathbf{x}(t), \tag{8}$$

where

$$\delta\mathbf{x}(t) = [\delta I1(t, 0), \dots, \delta I1(t, \tau_{ex}), \delta E(t, 0), \dots, \delta E(t, \tau_{in}), \delta I2(t, 0), \dots, \delta I2(t, \tau_{in}), \delta H(t, 0), \dots, \delta H(t, \tau_h), \delta D(t), \delta M(t, 0), \dots, \delta M(t, \tau_m)]^T,$$

and

$$\mathbf{A} = \begin{bmatrix} 0 & 0 & 0 & \dots & 0 & \alpha & \dots & \alpha & \alpha \\ \beta & 0 & 0 & \dots & 0 & 0 & \dots & 0 & 0 \\ 0 & \beta & 0 & \dots & 0 & 0 & \dots & 0 & 0 \\ \vdots & & \ddots & & & & & & \vdots \\ \vdots & & & \ddots & & & & & \vdots \\ \vdots & & & & \ddots & & & & \vdots \\ \vdots & & & & & \ddots & & & \vdots \\ \vdots & & & & & & \ddots & & \vdots \\ \vdots & & & & & & & \ddots & \vdots \\ 0 & 0 & 0 & \dots & 0 & 0 & & \bar{\beta} & 0 \end{bmatrix},$$

$$\mathbf{C} = \begin{bmatrix} 0 & 0 & \dots & 0 & \tau_{div}^{-1} & 0 & \dots & 0 & 0 \\ 1 & 0 & \dots & 0 & 0 & 0 & \dots & 0 & 0 \\ 0 & 1 & & 0 & 0 & 0 & \dots & 0 & 0 \\ \vdots & & \ddots & 0 & 0 & 0 & \dots & 0 & 0 \\ 0 & & & 1 & 1 - \tau_{div}^{-1} & 0 & \dots & 0 & 0 \\ 0 & & & & 0 & 0 & & 0 & 0 \\ 0 & & & & & 1 & & 0 & 0 \\ \vdots & & & & & & \ddots & & \vdots \\ 0 & & & & & & & 1 & 0 \end{bmatrix},$$

and

$$\mathbf{B} = \begin{bmatrix} 0 & \vdots & 0 & 0 & \vdots & 0 & 0 \\ 0 & \vdots & 0 & -\frac{\gamma_{inf}}{N}h & \vdots & -\frac{\gamma_{inf}}{N}h & -\frac{\gamma_{inf}}{N}h \\ \vdots & \vdots & \vdots & \vdots & \vdots & \vdots & \vdots \\ 0 & \vdots & 0 & -\frac{\gamma_{inf}}{N}h & \vdots & -\frac{\gamma_{inf}}{N}h & -\frac{\gamma_{inf}}{N}h \\ \tau_{lin}^{-1} & \vdots & \tau_{lin}^{-1} & \tau_{lin}^{-1} & \vdots & \tau_{lin}^{-1} & \bar{\beta} + \tau_{lin}^{-1} \\ 0 & \vdots & 0 & (1 + \gamma_m)\frac{\gamma_{inf}m}{N}V & \vdots & (1 + \gamma_m)\frac{\gamma_{inf}m}{N}V & (1 + \gamma_m)\frac{\gamma_{inf}m}{N}V \\ 0 & \vdots & 0 & 0 & \vdots & 0 & 0 \\ \vdots & \vdots & \vdots & \vdots & \vdots & \vdots & \vdots \end{bmatrix}$$

where

$$\begin{aligned} h &= P\hat{H}, \\ \alpha &= \gamma_{inf} \frac{\tau_h}{\tau_h + 1 + \tau_{div}}, \\ \beta &= 1 - \frac{1}{\tau_{lin}}, \\ \bar{\beta} &= \beta \left(1 - \frac{\gamma_{inf}mC}{N}\right). \end{aligned}$$

In matrix  $\mathbf{A}$ , from right-up to left-down, there are first  $\tau_{ex} + 1$   $\beta$ 's, then  $\tau_{in} + \tau_{lin} + 1$   $\bar{\beta}$ 's. Therefore, the characteristic matrix of the system at the virus-free equilibrium is reducible. The stability of the equilibrium is determined by the eigenvalues,  $\Lambda$ 's, of matrices  $\mathbf{A}$  and  $\mathbf{C}$ . Denote the maximal modulus of  $\Lambda$ 's by  $\Lambda_{max}$ . If  $\Lambda_{max} < 1$ , the equilibrium is stable; if  $\Lambda_{max} > 1$ , the equilibrium is unstable. If  $\Lambda_{max} = 1$ , the equilibrium is critical.

The matrix  $\mathbf{A}$  is a Leslie non-negative matrix whose eigenvalues satisfy

$$\Lambda^{\tau_{ex} + \tau_{in} + \tau_{lin} + 3} - \bar{\alpha}\bar{\beta}^{\tau_{ex} + \tau_{in} + \tau_{lin} + 2} \sum_{j=0}^{\tau_{lin}} \Lambda^j \bar{\beta}^{-j} = 0, \quad (9)$$

where  $\bar{\alpha} = \alpha(\beta/\bar{\beta})^{\tau_{ex} + 1}$ .

For the eigenvalues of matrix  $\mathbf{A}$ , we have the following

**Theorem 1:** For Eq. (9), when  $\bar{\alpha} \in [0, \infty)$  and  $\bar{\beta} \in [0, 1)$ , there is a  $\Lambda$  satisfying  $|\Lambda| > 1$  when  $\bar{\alpha} > \alpha_1 = \frac{1 - \bar{\beta}}{\bar{\beta}^{\tau_{ex} + \tau_{in} + 2}(1 - \bar{\beta}^{\tau_{lin} + 1})}$ .

*Proof.* Obviously, when  $\bar{\alpha} = 0$ ,  $\Lambda = 0$ . Because of the continuity, there is a  $\alpha_0 > 0$  so that when  $\bar{\alpha} < \alpha_0$ ,  $|\Lambda| < 1$ .

Let  $\Lambda = \rho e^{i\theta}$  where  $\rho \geq 0$ ,  $\theta \in [0, 2\pi)$  and  $i^2 = -1$ . Substituting it into Eq. (9), we have

$$(\rho e^{i\theta})^{\tau_{ex} + \tau_{in} + \tau_{lin} + 3} = \bar{\alpha}\bar{\beta}^{\tau_{ex} + \tau_{in} + \tau_{lin} + 2} \sum_{j=0}^{\tau_{lin}} \rho e^{ij\theta} \bar{\beta}^{-j}. \quad (10)$$

Assume that when  $\bar{\alpha} = \alpha_1$ ,  $|\Lambda| = \rho = 1$ . At  $\bar{\alpha} = \alpha_1$ , we have

$$= \frac{\cos(\tau_{ex} + \tau_{in} + \tau_{lin} + 3)\theta}{\alpha_1 \bar{\beta}^{\tau_{ex} + \tau_{in} + \tau_{lin} + 2} (1 + \bar{\beta}^{-1} \cos \theta + \dots + \bar{\beta}^{-\tau_{lin}} \cos \tau_{lin} \theta)}, \quad (11)$$

and

$$= \frac{\sin(\tau_{ex} + \tau_{in} + \tau_{lin} + 3)\theta}{\alpha_1 \bar{\beta}^{\tau_{ex} + \tau_{in} + \tau_{lin} + 2} (\bar{\beta}^{-1} \sin \theta + \bar{\beta}^{-2} \sin 2\theta + \dots + \bar{\beta}^{-\tau_{lin}} \sin \tau_{lin} \theta)}.$$

From Eqs. (11) and (12), we can solve  $\theta$  and  $\alpha_1$ . Obviously,  $\theta = 0$  is one of the solutions of  $\theta$ . Substituting  $\theta = 0$  into Eq. (11), we have

$$\alpha_1 = \frac{1 - \bar{\beta}}{\bar{\beta}^{\tau_{ex} + \tau_{in} + 2} (1 - \bar{\beta}^{\tau_{lin} + 1})}. \quad (12)$$

One can see that  $\alpha_1$  monotonically increases as  $\tau_{ex} + \tau_{in}$  does, but decreases as  $\tau_{lin}$  increases and when  $\tau_{lin} \rightarrow \infty$ ,  $\alpha_1 \rightarrow 0$ .

Next, the derivative of  $\rho$  with respect to  $\bar{\alpha}$  on Eq. (10) at  $\bar{\alpha} = \alpha_1$ , namely,  $\theta = 0$ ,  $\rho = 1$  yields

$$\left. \frac{\partial \rho}{\partial \bar{\alpha}} \right|_{\alpha_1} = \frac{\bar{\beta}^{\tau_{ex} + \tau_{in} + 2} \sum_{j=0}^{\tau_{lin}} \bar{\beta}^{\tau_{lin} - j}}{\tau_{ex} + \tau_{in} + \tau_{lin} + 3 - \alpha_1 \bar{\beta}^{\tau_{ex} + \tau_{in} + 2} \sum_{j=0}^{\tau_{lin}} j \bar{\beta}^{\tau_{lin} - j}}. \quad (13)$$

Therefore, when

$$\tau_{ex} + \tau_{in} + \tau_{lin} + 3 > \alpha_1 \bar{\beta}^{\tau_{ex} + \tau_{in} + 2} \sum_{j=0}^{\tau_{lin}} j \bar{\beta}^{\tau_{lin} - j}$$

or, by using Eq. (12),

$$(\tau_{ex} + \tau_{in} + 2) \sum_{j=0}^{\tau_{lin}} \bar{\beta}^j > - \sum_{j=0}^{\tau_{lin}} (j + 1) \bar{\beta}^j, \quad (14)$$

$\left. \frac{\partial \rho}{\partial \bar{\alpha}} \right|_{\alpha_1} > 0$ . Because Eq. (14) always holds for any value of parameters, at least one  $\Lambda$  in Eq. (9) is of  $|\Lambda| > 1$  when  $\bar{\alpha} > \alpha_1$ . This completes the proof.  $\square$

We note that  $\alpha_1$  may not be the first value of  $\bar{\alpha}$  for  $|\Lambda| = 1$  when  $\bar{\alpha}$  increases from 0. In this case,  $\alpha_0 < \alpha_1$ .

The eigenvalues of matrix  $\mathbf{C}$  satisfies

$$\Lambda^{\tau_m + 1} [\tau_{div}^{-1} + (1 - \tau_{div}^{-1} - \Lambda)\Lambda^{\tau_h + 1}] = 0. \quad (15)$$

Hence  $\Lambda$  equals to zero or satisfies

$$\tau_{div}^{-1} + (1 - \tau_{div}^{-1} - \Lambda)\Lambda^{\tau_h + 1} = 0, \quad (16)$$

for which we have the following

**Theorem 2:** When  $\tau_{div}^{-1} \in [0, 1]$  and  $\tau_h \geq 0$ , the possible maximal  $|\Lambda|$  for Eq. (16) is one.

*Proof.* Let  $\Lambda = \rho e^{i\theta}$  where  $\rho \geq 0$ ,  $\theta \in [0, 2\pi)$  and  $i^2 = -1$ . Substituting it into Eq. (16) and taking the norm (modulus squared) on the both sides, we have

$$\begin{aligned} \tau_{div}^{-2} &= |1 - \tau_{div}^{-1} - \rho \cos \theta - i\rho \sin \theta|^2 |\rho e^{i\theta}|^{2\tau_h + 2} \\ &= [(1 - \tau_{div}^{-1} - \rho \cos \theta)^2 + \rho^2 \sin^2 \theta] \rho^{2\tau_h + 2} \\ &= [(1 - \tau_{div}^{-1})^2 - 2\rho(1 - \tau_{div}^{-1}) + \rho^2 + 2\rho(1 - \tau_{div}^{-1}) - 2\rho(1 - \tau_{div}^{-1}) \cos \theta] \rho^{2\tau_h + 2} \\ &= [(1 - \tau_{div}^{-1} - \rho)^2 + 2\rho(1 - \tau_{div}^{-1})(1 - \cos \theta)] \rho^{2\tau_h + 2} \\ &\geq (\rho - 1 + \tau_{div}^{-1})^2 \rho^{2\tau_h + 2}. \end{aligned}$$

Assume  $\rho > 1$ , we have

$$\tau_{div}^{-2} > \tau_{div}^{-2},$$

which is not true, therefore  $|\Lambda| = \rho \leq 1$ .  $\square$

From the above analysis of the eigenvalues of matrices  $\mathbf{A}$  and  $\mathbf{C}$ , we can conclude that the stability of the virus-free equilibrium is determined by the eigenvalues of  $\mathbf{A}$ . When  $\bar{\alpha} > \alpha_1$  that satisfies Eq. (12), the equilibrium is unstable. Since  $\gamma_{infmm}c/N \ll 1$ , we have  $\bar{\alpha} \approx \alpha$  and  $\bar{\beta} \approx \beta$ . In our chosen parameter region, we then have

$$\begin{aligned}\alpha &= \frac{\gamma_{inf}\tau_h}{\tau_h+1+\tau_{div}} \approx 1.2, \\ \alpha_1 &= \frac{1-\beta}{\beta^{\tau_{ex}+\tau_{in}+2}(1-\beta^{\tau_{in}+1})} \approx 0.089.\end{aligned}$$

The virus-free equilibrium is unstable. Our numerical simulations show that when  $\alpha = 1.2$ , the system has a periodic solution which indicates that a Neimark-Sacker bifurcation [22] may occur for the system.

The analysis of the stability of the virus-persistent equilibrium is challenged due to the complexity of the system. In this case the characteristic matrix of the system is non-reducible, and the size of the matrix is too large for a formal analysis because of the age structure of the system variables. Instead, we use numerical simulations to test the stability. It is found that the equilibrium is unstable in the chosen parameter region, and can be stable in some parameter regions. If  $\gamma_{inf}$  is chosen as the bifurcation parameter, it is found that the system experiences from stable virus-free state to stable virus-persistent state and then to periodic state when  $\gamma_{inf}$  increases from 0.01 to 0.5 as shown in Fig. 3, and a Neimark-Sacker bifurcation occurs near  $\gamma_{inf} = 0.1$ .

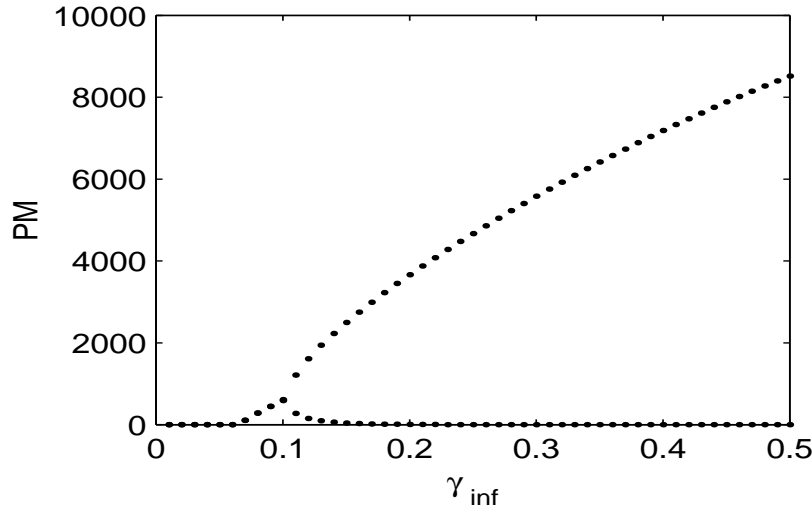


FIGURE 3. Bifurcation diagram of  $PM + PMM$  showing that our model system (1-7) is in virus-free equilibrium when  $\gamma_{inf} \in [0.01, 0.06)$ , in virus-persistent equilibrium when  $\gamma_{inf} \in (0.06, 0.1)$ , and in periodic state when  $\gamma_{inf} \in (0.1, 0.5]$ , a Neimark-Sacker bifurcation occurs near  $\gamma_{inf} = 0.1$ .

A more detailed numerical simulation shows that both the virus-free and virus-persistent equilibria are unstable when  $\gamma_{inf} > 0.1$  and the system is in a periodic or chaotic state. Since the parameter values in our model are estimated from experiment and the results of our model agree with some important experimental and

clinical observations during the effector stage, we may say that these parameter values are reasonable. An interesting question arises: How does the immune system, or more rigorously, our model system realize the memory stage from the effector stage? We notice that there are many possible ways to realize the memory stage, for instance, by considering the cross-reactive property of CTLs (Antia *et al.*, 1998) or by taking medicine (Wodarz and Lloyd, 2004). Here we give another maybe reasonable way by incorporating the function of antibodies into our model.

**4. The transform between the effector and memory stages.** The antibody is one of the immune substances. The variable,  $MM$ , in our model is for memory CTLs but not for antibodies because of their distinct functions: CTLs kill the expressing and infectious cells and antibodies bind virus particles so that the viruses lose their ability in infecting healthy cells. To express the function of antibodies in our lattice population model, we consider the spacial structure of tissue cells, or the lattices. In Eq. (1), we assumed that the growth rate of infected cells is  $\gamma_{inf}PI2/N$  where  $\gamma_{inf}$  is a constant. If we consider the function of antibodies in our model, this growth rate should be modified. Healthy epithelial cells are infected by the viruses (antigens) released from the infectious cells,  $PI2$ , and what we are interested in is how fast the healthy epithelial cells are infected because of  $PI2$ . It is assumed that the neutralized (bound) viruses (antigens) are unable to infect the healthy cells, and only the free(un-bound) viruses (antigens) are able to infect healthy cells (Ahmed *et al.*, 2002). If there are antibodies between the infectious and healthy cells, some antigens from the infectious cells will be bound by antibodies. Suppose that per hour, each infectious cell releases  $\alpha_{ag}$  antigens, and denote the total population of antibodies, antigens and bound antigens by  $Ab$ ,  $Ag$ ,  $(Ag)_b$  respectively. According to Bell's work (1970, 1971, 1973), the number of un-bound antigens that may reach the healthy cells per hour is

$$Ag - (Ag)_b = \alpha_{ag}PI2\left(1 - \frac{kAb}{1 + k(Ab + \alpha_{ag}PI2)}\right) = \alpha_{ag}\frac{1 + k\alpha_{ag}PI2}{1 + kAb + k\alpha_{ag}PI2}PI2, \tag{17}$$

where  $k$  is usually a small constant. If the infection rate of healthy cells is proportional to the number of un-bound antigens, we may have the form of the infection rate as

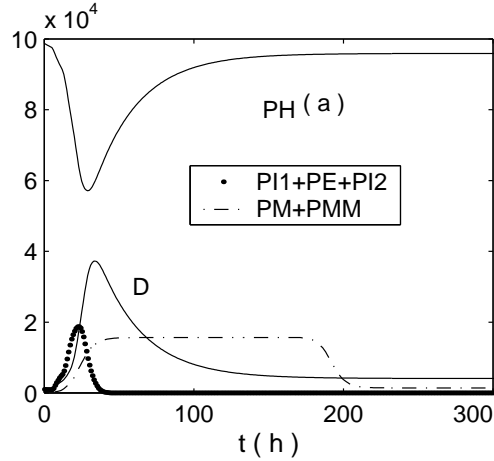
$$\gamma_{inf} = \gamma_0\frac{1 + k\alpha_{ag}PI2}{1 + kAb + k\alpha_{ag}PI2}, \tag{18}$$

where  $\gamma_0$  is a constant, and can be further rewritten as

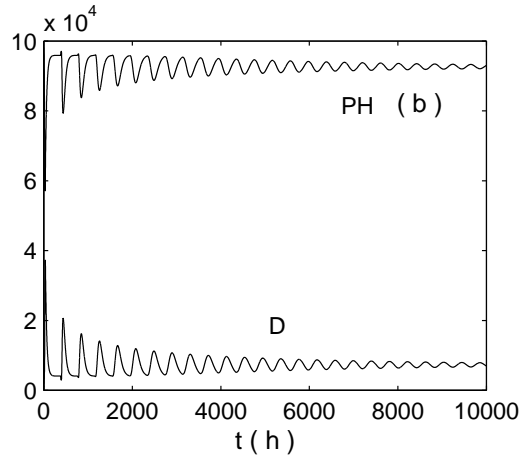
$$\gamma_{inf} = \gamma_0\frac{pq + PI2}{q + PI2}, \tag{19}$$

where  $p = \frac{1}{1+kAb}$ ,  $q = \frac{1+kAb}{k\alpha_{ag}}$ , and  $\gamma_0 = 1.3$  as the listed  $\gamma_{inf}$  in Table 1.  $\gamma_0$  describes the characteristic of the virus in infection tissue cells, and therefore its value does not change during the immune process (in practice,  $\gamma_0$  may change because of the virus mutation), but the part,  $\frac{pq+PI2}{q+PI2}$ , standing for the competition between the antigen and antibody, could vary with time. Since  $p \in [0, 1)$ ,  $\gamma_{inf}$  decreases as  $q$  increases. We assumed that  $\gamma_{inf}$  is proportional to the rate of un-bound antigens over total antigens. Thus, when  $q$  increases, more antigens are bound by antibodies. In other words, the strong ability of antibodies in binding antigens will cause a big value of  $q$ , and therefore a small value of  $\gamma_{inf}$ . From Fig. 3, one can see that a small value of  $\gamma_{inf}$  will result in the formation of memory stage. Similarly, the

smaller  $p$ , the smaller  $\gamma_{inf}$ , the easier the formation of the memory stage. On the other hand, the weak ability of antibodies will cause the difficulty of memory stage formation. Therefore, the interaction between antigens and antibodies via tissue cells plays an essential role in realizing the memory stage. This result is consistent with the recent experimental findings on the important role of antibody in the immune process (Ahmed *et al.*, 2002).



(a)



(b)

FIGURE 4. (a) The same as Fig. 2(a) except that  $\gamma_{inf}$  is the monotonic function, (19). (b) The evolution of  $PH$  and  $D$ .  $p = 0.04$  and  $q = 0.002N$ .

Particularly, if we take  $p = 0.04$ , when  $PI2$  tends to 0 and  $\infty$ ,  $\gamma_{inf}$  tends to, respectively, 0.052 and 1.3 so that the immune system is, respectively, in the stable virus-free equilibrium and periodic states. The value of  $q$  affects the slope of the monotonic function,  $\gamma_{inf}$ , and is relative to  $N$ . When  $q = 0.002N$ , the system has both the effector stage and memory stage as shown in Fig. 4 and Fig. 5(a). It is

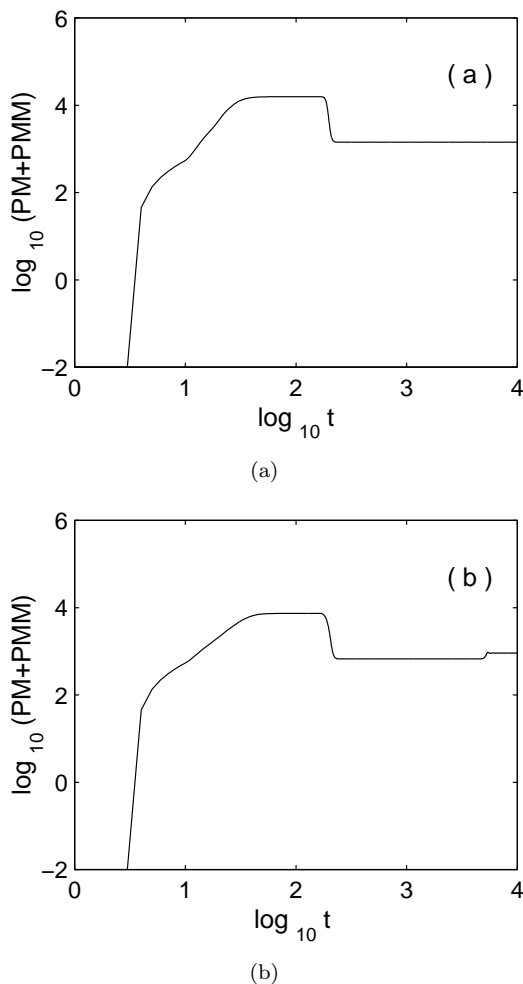


FIGURE 5. The evolution of  $PM+MM$  when  $\gamma_{inf}$  is the monotonic function, (19), where the memory stage is in (a) stable virus-free equilibrium state when  $p = 0.04$ ,  $q = 0.002N$ , and (b) first unstable virus-free equilibrium and then stable virus-persistent equilibrium states when  $p = 0.06$ ,  $q = 0.04N$ .

observed from Fig. 4(a) that the dynamical behavior of the system in the effector stage is similar to that when  $\gamma_{inf}$  is fixed at 1.3 as shown in Fig. 2(a), and the memory stage is formed when  $t > 200h$  (see Fig. 5(a)). If  $p = 0.06$  and  $q = 0.04N$  the system is in the virus-persistent memory stage as shown in Fig. 5(b). When  $\gamma_{inf}$  is a step function, we obtained very similar results.

It is believed that other monotonic functions of  $\gamma_{inf}$  such as the recognition probability function (Perelson & Oster, 1979) and the standard neuron feedback function (Yao *et al.*, 2001) would work well too. Further, it may also be interesting to investigate the role of CTLs ( $= PM + PMM$  in our model) in the formation of memory stage for our model system. To do this, we fix  $\gamma_{inf} = 1.3$  and adjust  $\gamma_{infm}$

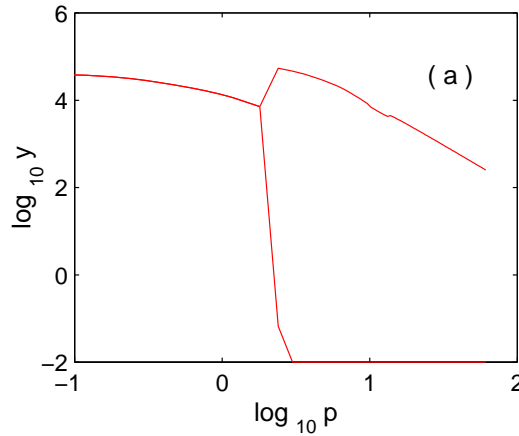
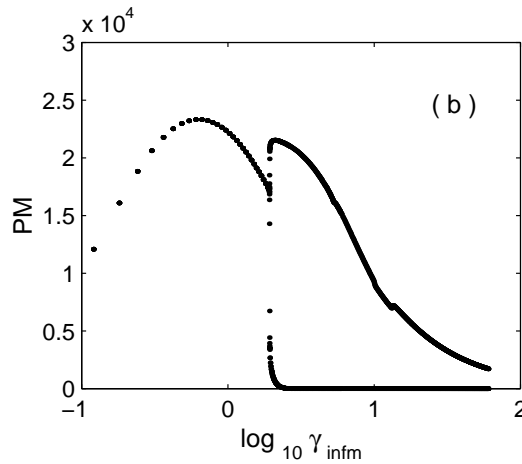
(a) virus-containing cells ( $= PI1 + PE + PI2$ )(b) CTLs ( $= PM + PMM$ )

FIGURE 6. Bifurcation diagram showing the role of CTLs ( $= PM + PMM$ ) in infection control:  $\gamma_{infm}$ , increases from 0.01 to 70 to simulate the various strength of CTLs.

to obtain the bifurcation diagrams of virus-containing cells ( $= PI1 + PE + PI2$ ) and CTLs ( $= PM + PMM$ ) as depicted in Fig. 6. It follows from the diagram that when  $\gamma_{infm} < 2h^{-1}$ , the system is in virus-persistent equilibrium, and the number of virus-containing cells is rather high. Also, comparing Fig. 6(a) with (b) in this regime ( $\gamma_{infm} < 2$ ), we find that there is a negative correlation between the virus-containing cells and CTLs when  $\gamma_{infm} < 0.3$ , and after that, a positive correlation. In experiments, both the negative and positive correlations have been observed (Ogg *et al.*, 1998, Wodarz, 2001b) and studied by Bangham *et al.* (1999) and Wodarz and Nowak (2000c). When  $\gamma_{infm} > 2$ , the system is in periodic state. As  $\gamma_{infm}$  increases, the number of CTLs decreases and from Fig. 6(a), the number of infected cells decreases slightly. This is because the generation of mature immune cells



needs the stimulation from viruses. When  $\gamma_{infm}$  increases, the viruses can be killed more efficiently resulting in less chance for virgin immune cells to be stimulated. This indicates that the strength of CTLs,  $(\gamma_{infm}PM + \gamma_{infmm}PMM)/N$ , is easily saturated resulting in the limited role of CTLs in the clearance of viruses, even though the memory CTLs are considered.

The above numerical simulations suggests that a Neimark-Sacker bifurcation occurs in the new model system too. The results also seem to suggest that in the absence of a humoral response there would be no cellular memory. In fact this is not correct. Recent experiments have confirmed that unlike antibodies, CTLs are cross-reactive (Antia *et al.*, 1998). If we consider this property of CTLs, the form of  $f$  in Eqs. (3) and (4) should be updated by  $f(PM, PMM, z) = 1 - \frac{\gamma_{infm}}{N}PM - \frac{\gamma_{infmm}}{N}PMM - z$ , where  $z$  represents the strength of those CTLs generated by the stimulation from the other kinds of viruses. Because  $z$  is an external variable, independent on the number of virus-containing cells ( $= PI1 + PE + PI2$ ), when it is strong enough, it can clear out the virus-containing cells and the memory stage can form even if there are no antibodies. However, the unique importance of antibodies in the infection control cannot be ignored even if there are strong cross-reactive CTLs. In addition, when  $\gamma_{inf}$  is not a fixed constant but a function of  $PI2$ , in our numerical simulations we need not enforce the condition that if  $PI1 < 10^{-16}$ ,  $PI1 = 0$  because either the virus-free or the virus-persistent equilibrium in the memory stage is stable. Thus, we can solve the problems of unstable equilibrium and no memory stage in our model by letting  $\gamma_{inf}$  be a reasonable function of  $PI2$ .

**5. Discussions.** The immune system can be taken as a complicated control system. It evolves to incorporate the tissue cell infection process. During the effector stage, the immune system might be in a non-equilibrium state so that the number of specific immune cells increases more rapidly to deal with the infectious tissue cells and viruses, while during the memory stage, the system is in a stable equilibrium or quasi-equilibrium state. In this paper, we have built a mathematical model to investigate how the immune system realizes the transformation from the periodic state to the equilibrium state. The model considers the interaction between the immune cells and tissue cells, and is at least partially validated by using influenza A virus data. The simulations agree with some important clinical observations. We have shown that the infection rate of healthy epithelial cells significantly effects the dynamical behavior of the immune system, and should be taken as a function of the concentration of infectious cells so that the both the effector stage and the memory stage can be realized. Thus, our work indicates the necessity to consider the effect of complicated forms of viruses, or complicated interaction between tissue cells and immune cells, on the dynamical behavior of the immune system. Our work also suggests that if a dynamical process of such a system as the immune system and the control system of SARS (Webb *et al.*, 2004) involves more than one stage, the underlying mathematical model for the system could have a non-constant parameter, and the dependence of this parameter on system's states plays an important role in transforming the system between different stages.

For both the two model systems, numerical simulations suggest the existence of the Neimark-Sacker bifurcation. A systematic and analytical study of the bifurcation in the model systems is interesting and essential, and we leave it for future work.

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