MATHEMATICAL BIOSCIENCES
AND ENGINEERING
Volume **3**, Number **1**, January **2006**

http://www.mbejournal.org/

pp. **237–248**

AN IMPROVED MODEL OF T CELL DEVELOPMENT IN THE THYMUS AND ITS STABILITY ANALYSIS

Hongjing Shi

Department of Mathematics and Mechanics, Applied Science College
University of Science and Technology Beijing
Beijing 100083, China

Wanbiao Ma

Department of Mathematics and Mechanics, Applied Science College
University of Science and Technology Beijing
Beijing 100083, China

Abstract. Based on some important experimental dates, in this paper we shall introduce time delays into Mehrs's non-linear differential system model which is used to describe proliferation, differentiation and death of T cells in the thymus (see, for example, [3], [6], [7] and [9]) and give a revised nonlinear differential system model with time delays. By using some classical analysis techniques of functional differential equations, we also consider local and global asymptotic stability of the equilibrium and the permanence of the model.

In honor of Professor Zhien Ma's 70th birthday

1. **Introduction.** It is well known [3], [6], [7] and [9] that the T lymphocyte compartment includes two types of T cell subpopulations, characterized according to their functions and distinct cell membrane markers. Helper and inducer T cells (expressing the CD4 marker) regulate the function of the other immunocytes. Cytotoxic and suppressor T cells (expressing the CD8 marker) destroy virally infected cells and foreign transplants. The development, differentiation and selection of T cells in the thymus are complex processes. Based on the data gained from experiments on mice by Finkel et al., Mehr et al. obtained the following non-liner differential system model to describe proliferation, differentiation and death of T cells in the thymus [6],[7]:

$$\left\{\begin{array}{lcl} \dot{N}(t) &=& (1-\frac{N(t)}{K_n})[s+r_nN(t)]-(d_n+s_n)N(t), \\ \dot{P}(t) &=& s_nN(t)+(1-\frac{Z}{K})r_pP(t)-(d_p+s_p)P(t), \\ \dot{P_s}(t) &=& s_pP(t)+(1-\frac{Z}{K})r_{ps}P_s(t)-(d_{ps}+s_4+s_8)P_s(t), \\ \dot{M_4}(t) &=& s_4P_s(t)+(1-\frac{Z}{K})r_4M_4(t)-(d_4+s_{04})M_4(t), \\ \dot{M_8}(t) &=& s_8P_s(t)+(1-\frac{Z}{K})r_8M_8(t)-(d_8+s_{08})M_8(t), \end{array}\right. \tag{1}$$

here N represents double-negative(DN) cells, and P represents double-positive(DP) cells that are not sensitive to deletion. The variable P_s represents DP cells that are sensitive to deletion, M_4 and M_8 are T_4 cells and T_8 cells, and $Z \equiv N + P + P_s +$

2000 *Mathematics Subject Classification.* Primary 92D30, Secondary 92D25,34K20.
Key words and phrases. T cells, quasi-steady-state approximation, time delay, transcendental equation, stability, permanence.

$M_4 + M_8$ is the total thymic population. The percentages of cells in the various sub-populations are defined by

$$DN \equiv \frac{N}{Z}, \quad DP \equiv \frac{P+P_s}{Z}, \quad CD_4 \equiv \frac{M_4}{Z}, \quad CD_8 \equiv \frac{M_8}{Z}.$$

In each equation of (1), there is an input term that is the rate of entry of cells from the previous compartment, except for the first equation, where we use s, the rate of seeding of T cell progenitor cells from the bone marrow. The s_j parameters represent maturation rates, that is, the rate of passage from one compartment to the next, except for s_{04} and s_{08}, which represent rates of export of mature T cells from the thymus. The r_i parameters represent cell division rates, and d_i parameters represent death rates, including the death of cells not rescued by positive selection and cell deletion due to negative selection. Based on the analysis of paper [6], competition occurs during seeding and early development of thymocytes; hence, there is an upper bound for the DN cells, denoted here by K_n. Due to the environmental restriction, there is also an upper bound for the total number of cells in thymus, denoted here by K. It is clear that competition in (1) is taken as the logistic form.

With the help of computer simulations, the authors of [6] and [7] show that the model (1) gives a better estimations of the experimental results for the total number of thymus cells and the fractions of various types of immature and mature thymocytes. Recently, based on stability theory of ordinary differential equations, Jin and Ma [3] gave a detailed theoretical analysis of the global asymptotic stability of the positive equilibrium of (1).

2. **Statement of the Improved Model and Boundedness of Solutions.** It is known that the differentiation of T cells in the thymus is complicated, and it will take some time to move from one compartment to the next compartment. It is estimated that the period of DN needs 14 days, DP needs 3 to 4 days, and that SP needs 7 to 14 days (see, for example, [1] and [8]). The facts imply that it is very important to introduce time delays in model (1). Hence, we have the following revised non-linear differential system model with time delays,

$$\begin{cases} \dot{N}(t) &= (1-\frac{N(t)}{K_n})[s+r_nN(t)] - c_0N(t), \\ \dot{P}(t) &= s_nN(t-\tau_1) + (1-\frac{Z}{K})r_pP(t) - c_1P(t), \\ \dot{P}_s(t) &= s_pP(t-\tau_2) + (1-\frac{Z}{K})r_{ps}P_s(t) - c_2P_s(t), \\ \dot{M}_4(t) &= s_4P_s(t-\tau_3) + (1-\frac{Z}{K})r_4M_4(t) - c_3M_4(t), \\ \dot{M}_8(t) &= s_8P_s(t-\tau_3) + (1-\frac{Z}{K})r_8M_8(t) - c_4M_8(t), \end{cases} \tag{2}$$

where $t \geq t_0$, $c_0 = s_n + d_n > 0$, $c_1 = s_p + d_p > 0$, $c_2 = d_{ps} + s_4 + s_8 > 0$, $c_3 = d_4 + s_{04} > 0$, and $c_4 = d_8 + s_{08} > 0$.

By biological meaning, the initial condition of (2) is given as

$$\begin{cases} N(t) &= \varphi_1(t) > 0, \\ P(t) &= \varphi_2(t) > 0, \\ P_s(t) &= \varphi_3(t) > 0, \\ M_4(t) &= \varphi_4(t) > 0, \\ M_8(t) &= \varphi_5(t) > 0, \end{cases} \tag{3}$$

where $\varphi_1(t)$,$\varphi_2(t)$,$\varphi_3(t)$,$\varphi_4(t)$ and $\varphi_5(t)$ are all continuous functions on $[t_0-\tau_1, t_0]$. With a standard argument, it is easily shown that the solution ($N(t)$, $P(t)$, $P_s(t)$,

$M_4(t)$, $M_8(t))$ of (2) with (3) is existent, positive and bounded on $[t_0, +\infty)$. Thus the following result easily can be proved.

Theorem 1. *The solution* $(N(t), P(t), P_s(t), M_4(t), M_8(t))$ *of* (2) *with* (3) *is existent, positive and bounded on* $[t_0, +\infty)$.

3. **Quasi-Steady-State Approximation and Reduction of Model.** It is clear that to give a theoretical analysis on the asymptotic properties of the nonlinear higher dimensional system (2) is rather difficult, since the simulations show that the time evolution of the more mature thymocyte subsets (P_s, M_4, M_8) follows that of P. Hence, we may be able to use the quasi-steady-state approximation as in [6]-[7] for P_s, M_4 and M_8, and assume that

$$\dot{P}_s(t) = \dot{M}_4(t) = \dot{M}_8(t) = 0.$$

Furthermore, note that given the typical parameter values given in [6]-[7], correspond to the total number of the cells $Z << K$. Hence, we may assume that $1 - Z/K \approx 1$. Therefore,

$$\begin{cases} P_s(t) &=& \frac{s_p}{c_2 - r_{ps}} P(t-\tau_2), \\ M_4(t) &=& \frac{s_p s_4}{(c_2-r_{ps})(c_3-r_4)} P(t-\tau_2-\tau_3), \\ M_8(t) &=& \frac{s_p s_8}{(c_2-r_{ps})(c_4-r_8)} P(t-\tau_2-\tau_3). \end{cases} \tag{4}$$

We further assume that

$$\frac{s_p}{c_2 - r_{ps}} > 0, \ \frac{s_p s_4}{(c_2-r_{ps})(c_3-r_4)} > 0, \ \frac{s_p s_8}{(c_2-r_{ps})(c_4-r_8)} > 0.$$

Hence, we have the following two-dimensional nonlinear delayed differential system for $N(t)$ and $P(t)$:

$$\begin{cases} \dot{N}(t) &=& (1 - \frac{N(t)}{K_n})[s + r_n N(t)] - c_0 N(t), \\ \dot{P}(t) &=& s_n N(t-\tau_1) + r_p P(t) - \frac{r_p}{K} N(t)P(t) - \frac{r_p s_p}{K(c_2-r_{ps})} P(t)P(t-\tau_2) \\ && -\frac{r_p}{K} P^2(t) - \frac{r_p G}{K} P(t)P(t-\tau_2-\tau_3) - c_1 P(t), \end{cases} \tag{5}$$

for $t \geq t_0$, where

$$G = \frac{s_p}{c_2 - r_{ps}} \left(\frac{s_4}{(c_3 - r_4)} + \frac{s_8}{(c_4 - r_8)}\right) > 0.$$

Let

$$\alpha = \frac{r_p}{K}, \ \beta = \frac{s_p}{c_2 - r_{ps}}, \ \gamma = \frac{1}{K_n},$$

then (5) is equivalent to

$$\begin{cases} \dot{N}(t) &=& (1 - \gamma N(t))[s + r_n N(t)] - c_0 N(t), \\ \dot{P}(t) &=& s_n N(t-\tau_1) + r_p P(t) - \alpha N(t)P(t) - \alpha P^2(t) - \alpha\beta P(t)P(t-\tau_2) \\ && -\alpha G P(t)P(t-\tau_2-\tau_3) - c_1 P(t), \end{cases} \tag{6}$$

for $t \geq t_0$.

In the following sections, we shall give a detailed analysis on local and global asymptotic stability of the equilibrium and permanence of (6).

As usual, the initial condition is given as

$$\begin{cases} N(t) &=& \varphi_1(t) > 0, \\ P(t) &=& \varphi_2(t) > 0, \ t \in [t_0 - \tau_1, t_0], \end{cases} \tag{7}$$

where $\varphi_1(t)$ and $\varphi_2(t)$ are continuous functions on $[t_0, +\infty)$.

We have the following.

Theorem 2. *The solution* $(N(t), P(t))$ *of* (6) *with* (7) *is existent, positive and bounded on* $[t_0, +\infty)$.

Proof. From $\varphi_i(t) > 0$ $(i = 1, 2)$ and the local existence theory of solutions (see, for example, [2], [4] and [10]), we can assume that $N(t)$ and $P(t)$ are all existent on $[t_0, b)$ $(t_0 < b < +\infty)$. Now, let us first show that $N(t) > 0$ $(t \geq t_0)$. The first equation of (6) is equivalent to

$$\dot{N}(t) = -\gamma r_n N^2(t) + (r_n - \gamma s - c_0)N(t) + s. \tag{8}$$

In fact, note that $\varphi_1(t) > 0$ $(t \in [t_0 - \tau_1, t_0])$ and the continuity of $N(t)$, if there is $t_1 \in [t_0, b)$ such that

$$N(t_1) = 0,\ N(t) > 0,\ (t_0 \leq t < t_1);$$

hence, $\dot{N}(t_1) \leq 0$. On the other hand, from (8) we have

$$\dot{N}(t_1) = -\gamma r_n N^2(t_1) + (r_n - \gamma s - c_0)N(t_1) + s = s > 0,$$

which is a contradiction to $\dot{N}(t_1) \leq 0$. Hence, $N(t) > 0$ for any $t \in [t_0, b)$.

Let us further show that $N(t)$ is also bounded on $[t_0, b)$. From (8), it follows that

$$\dot{N}(t) = -\gamma r_n [N(t) - N_1][N(t) - N_2], \tag{9}$$

where N_1 and N_2 $(N_1 < 0, N_2 > 0)$ are two real roots of the equation

$$-\gamma r_n N^2 + (r_n - \gamma s - c_0)N + s = 0.$$

Since the first equation of system (6) is a standard scalar ordinary differential equation which satisfies uniqueness of solutions, it is easily shown that

$$N(t) \leq N_A = max(N(t_0), N_2)$$

for any $t \in [t_0, b)$. The boundedness of $N(t)$ on $[t_0, b)$, together with the continuous extension theory of solutions (see, for example, [2], [4] and [10]), shows that $N(t)$ is existent and positive on $[t_0, +\infty)$, and satisfies $N(t) \leq N_A = max(N(t_0), N_2)$ for any $t \in [t_0, +\infty)$.

Next, we will show that $P(t)$ is existent, positive and bounded on $[t_0, +\infty)$ for any $t > t_0$.

We first show that $P(t) > 0$ for any $t \in [t_0, b)$. If not, also by $\varphi_2(t) > 0$ $(t_0 - \tau_1 \leq t \leq t_0)$ and continuity of $P(t)$, there is $t_2 \in [t_0, b)$ such that

$$P(t_2) = 0,\ P(t) > 0,\ (t_0 \leq t < t_2).$$

Hence, $\dot{P}(t_2) \leq 0$. However, from (6),

$$\dot{P}(t_2) \quad = \quad s_n N(t_2 - \tau_1) > 0,$$

which is a contradiction to $\dot{P}(t_2) \leq 0$. Hence, $P(t) > 0$ for any $t \in [t_0, b)$.

Let us further show that $P(t)$ is bounded on $[t_0, b)$. In fact, we have from (6) that

$$\dot{P}(t) \leq -\alpha P^2(t) + r_p P(t) + s_n N_B,$$

for $t \in [t_0, b)$, where $N_B = max\{N_2, \sup_{t_0 - \tau_1 \leq t \leq t_0} \varphi_1(t)\}$. Based on the well known comparison principle (see, for example, [5]), it is easy to show that $P(t)$ is also bounded on $[t_0, b)$. Hence, the continuous extension theory of solutions shows that $N(t)$ and $P(t)$ are existent, positive and bounded on $[t_0, +\infty)$. The proof of Theorem 2 is completed.

4. **Local Asymptotic Stability of (6).** In this section, we shall consider the local asymptotic stability of the positive equilibria of (6). Let $(N(t), P(t)) = (N^*, P^*)$ be the only positive equilibrium of (6); then it has

$$\left\{\begin{array}{l} (1-\gamma N(t))[s+r_n N(t)] - c_0 N(t) = 0, \\ s_n N(t) + r_p P(t) - \alpha N(t)P(t) - \alpha P^2(t) - \alpha\beta P(t)P(t) \\ -\alpha G P(t)P(t) - c_1 P(t) = 0. \end{array}\right. \tag{10}$$

From the first equation of (10), we have

$$N^* = \frac{-(r_n - \gamma s - c_0) - \sqrt{(r_n-\gamma s - c_0)^2 + 4\gamma r_n s}}{-2\gamma r_n} > 0.$$

From the second equation of (10),

$$P^* = \frac{\delta + \sqrt{\delta^2 + 4\alpha(G'+1)s_n N^*}}{2\alpha(G'+1)} > 0,$$

where

$$G' = G + \beta > 0,\ \delta = r_p - \alpha N^* - c_1.$$

We have the following.

Theorem 3. *The positive equilibrium* (N^*, P^*) *of* (6) *is locally asymptotically stable for any time delays* τ_1, τ_2, *and* τ_3.

Proof. Let

$$\left\{\begin{array}{l} u(t) = N(t) - N^*, \\ v(t) = P(t) - P^*, \end{array}\right. \tag{11}$$

then, (6) is equivalent to

$$\left\{\begin{array}{lll} \dot{u}(t) &=& (r_n - \gamma s - c_0 - 2\gamma r_n N^*)u(t) - \gamma r_n u^2(t), \\ \dot{v}(t) &=& -\alpha P^* u(t) + s_n u(t-\tau_1) + (r_p - \alpha N^* - 2\alpha P^* - \alpha\beta P^* - \alpha P^* G, \\ && -c_1)v(t) - \alpha\beta v(t)v(t-\tau_2) - \alpha G v(t)v(t-\tau_2-\tau_3) - \alpha\beta P^* v(t-\tau_2), \\ && -\alpha P^* G v(t-\tau_2-\tau_3) - \alpha u(t)v(t) - \alpha v^2(t), \end{array}\right. \tag{12}$$

and its corresponding linearized system is

$$\left\{\begin{array}{lll} \dot{u}(t) &=& (r_n - \gamma s - c_0 - 2\gamma r_n N^*)u(t), \\ \dot{v}(t) &=& -\alpha P^* u(t) + s_n u(t-\tau_1) + (r_p - \alpha N^* - 2\alpha P^* - \alpha\beta P^* - \alpha P^* G \\ && -c_1)v(t) - \alpha\beta P^* v(t-\tau_2) - \alpha P^* G v(t-\tau_2-\tau_3). \end{array}\right. \tag{13}$$

The associated characteristic equation of (13) is given by

$$[\lambda - (r_n - \gamma s - c_0 - 2\gamma r_n N^*)][\lambda - (r_p - \alpha N^* - 2\alpha P^* - \alpha\beta P^* - \alpha G P^* - c_1)$$
$$+\alpha\beta P^* e^{-\tau_2\lambda} + \alpha G P^* e^{-(\tau_2+\tau_3)\lambda}] = 0.$$

Obviously, it has one negative characteristic root

$$\begin{array}{lll} \lambda = \lambda_1 &=& r_n - \gamma s - c_0 - 2\gamma r_n N^* \\ &=& -\sqrt{(r_n - \gamma s - c_0)^2 + 4\gamma r_n s} < 0. \end{array}$$

Now, let us consider the transcendental equation

$$\lambda - (r_p - \alpha N^* - 2\alpha P^* - \alpha\beta P^* - \alpha G P^* - c_1) + \alpha\beta P^* e^{-\tau_2\lambda} + \alpha G P^* e^{-(\tau_2+\tau_3)\lambda} = 0. \tag{14}$$

By the second equation of (10),

$$s_n N^* + r_p P^* - \alpha N^* P^* - \alpha P^{*2} - \alpha\beta P^{*2} - \alpha G P^{*2} - c_1 P^* = 0, \tag{15}$$

which implies

$$\alpha N^* + \alpha P^* + \alpha\beta P^* + \alpha G P^* + c_1 - r_p = s_n \frac{N^*}{P^*}.$$

Hence,

$$\begin{aligned} a^* &= -(r_p - \alpha N^* - 2\alpha P^* - \alpha\beta P^* - \alpha G P^* - c_1) \\ &= s_n \frac{N^*}{P^*} + \alpha P^* > 0, \end{aligned}$$

$$b = \alpha\beta P^* > 0, \ c = \alpha G P^* > 0.$$

Let $a = -(r_p P^* - \alpha N^* - 2\alpha P^* - c_1)$, then

$$a^* = a + b + c.$$

The transcendental equation (14) is equivalent to

$$\lambda + (a + b + c) + be^{-\tau\lambda} + ce^{-\mu\lambda} = 0, \tag{16}$$

where $\tau = \tau_2$ and $\mu = \tau_2 + \tau_3$.

When $\mu = \tau = 0$, equation (16) reduces to

$$\lambda + (a + b + c) + b + c = 0.$$

Thus

$$\lambda = \lambda_2 = -a - 2(b + c) < 0.$$

This shows that (N^*, P^*) of (6) is locally asymptotically stable for $\tau_2 = \tau_3 = 0$.

If (16) has pure imaginary root $\lambda = iw$ $(w > 0)$ for $\tau + \mu > 0$, we have from (16) that

$$iw + (a + b + c) + bcos\tau w - ibsin\tau w + ccos\mu w - icsin\mu w = 0. \tag{17}$$

Separating the real part from the imaginary part, we have

$$\begin{cases} bcos\tau w + ccos\mu w = -(a + b + c), \\ bsin\tau w + csin\mu w = w. \end{cases} \tag{18}$$

Hence,

$$b^2 + c^2 + 2bccos(\mu - \tau)w = (a + b + c)^2 + w^2,$$

which implies that

$$cos(\tau - \mu)w = \frac{a^2 + w^2 + 2ab + 2bc + 2ac}{2bc} > \frac{2bc}{2bc} = 1.$$

Clearly, this is a contradiction. Because the roots of the transcendental equation (16) continuously depend on μ and τ (see, for example, [4]), and the roots of (16) have negative real parts for $\mu = \tau = 0$, all roots of (14) must have negative real parts for any time delay. Hence, (N^*, P^*) of (6) is locally asymptotically stable for any time delay. The proof of Theorem 3 is complete.

5. **Permanence and Global Asymptotic Stability.** In this section, we shall further consider the global asymptotic stability of the positive equilibrium (N^*, P^*) of (6) and permanence of (6).

First, let us consider equation (9) and define a Liapunov function V as below,

$$V(N) = \frac{1}{2}(N - N^*)^2.$$

Obviously, $V(N)$ is positive definite and has the property of infinity with respect to $N - N^*$. The derivative along the solution of (9) is

$$\frac{dV}{dt} = -\gamma(N(t) - N_1^*)(N(t) - N^*)^2,$$

from which it follows that dV/dt is negative definite with respect to $N - N^*$. Thus, it follows from Liapunov global asymptotic stability theorem that $N(t) = N^*$ is the globally asymptotically stable equilibrium of the first equation of (6).

Next, let us discuss attractiveness of $P(t) = P^*$.

Note that

$$\lim_{t\to+\infty} N(t) = N^*,$$

for any $\epsilon > 0$, there exists $T_1 > t_0$ such that for any $t \geq T_1$,

$$N^* - \epsilon < N(t) < N^* + \epsilon.$$

By the second equation of (6) and $P(t) > 0$ ($t \in [t_0, +\infty)$),

$$\dot{P}(t) \leq -\alpha P^2(t) + r_p P(t) + s_n(N^* + \epsilon)$$

for any $t \geq T_1$. Let us consider the comparison system,

$$\dot{P}_1(t) = -\alpha P_1^2(t) + r_p P_1(t) + s_n(N^* + \epsilon), \ P_1(T_1) = P(T_1) > 0. \tag{19}$$

Using the same discussion as for $N(t)$, it is easy to see that $P_1(t) > 0$ on $[T_1, +\infty)$ and that

$$\lim_{t\to+\infty} P_1(t) = P_1^*,$$

where P_1^* is positive equilibrium of (19), and

$$P_1^* = \frac{r_p + \sqrt{r_p^2 + 4\alpha s_n(N^* + \epsilon)}}{2\alpha} > 0.$$

Thus, by the well known comparison principle,

$$\limsup_{t\to+\infty} P(t) \leq \lim_{t\to+\infty} P_1(t) = P_1^*.$$

Hence, there exists $T_2 > T_1$ such that for $t \geq T_2$,

$$P(t) < P_1^* + \epsilon.$$

By the second equation of (6),

$$\begin{aligned}
\dot{P}(t) \quad &\geq \quad s_n(N^* - \epsilon) + r_p P(t) - \alpha(N^* + \epsilon)P(t) - \alpha P^2(t) - \alpha\beta(P_1^* + \epsilon)P(t) \\
&\qquad -\alpha G(P_1^* + \epsilon)P(t) - c_1 P(t) \\
&= \quad -\alpha P^2(t) + [r_p - \alpha(N^* + \epsilon) - \alpha\beta(P_1^* + \epsilon) - \alpha G(P_1^* + \epsilon) - c_1]P(t) \\
&\qquad +s_n(N^* - \epsilon) \\
&= \quad -\alpha[P(t) - \bar{P}_1^*][P(t) - \bar{Q}_1^*],
\end{aligned}$$

where $\bar{P}_1^*$ and $\bar{Q}_1^*$ are two equilibria of the following comparison system

$$\begin{cases} \dot{\bar{P}}_1(t) = & -\alpha\bar{P}_1^2(t) + [r_p - \alpha(N^* + \epsilon) - \alpha\beta(P_1^* + \epsilon) - \alpha G(P_1^* + \epsilon) - c_1]\bar{P}_1(t) \\ & +s_n(N^* - \epsilon), \\ \bar{P}_1(T_2) = & P(T_2) > 0, \end{cases} \tag{20}$$

where $\bar{Q}_1^* < 0$ and

$$\begin{aligned} \bar{P}_1^* &= \frac{[r_p - \alpha(N^* + \epsilon) - \alpha\beta(P_1^* + \epsilon) - \alpha G(P_1^* + \epsilon) - c_1]}{2\alpha} \\ &\quad + \frac{\sqrt{[r_p - \alpha(N^* + \epsilon) - \alpha\beta(P_1^* + \epsilon) - \alpha G(P_1^* + \epsilon) - c_1]^2 + 4\alpha s_n(N^* - \epsilon)}}{2\alpha} \\ &> 0. \end{aligned}$$

It also follows that $\bar{P}_1(t) > 0$ for $t \in [T_2, +\infty)$ and that the positive equilibrium $\bar{P}_1^*$ of (20) is also global asymptotically stable. Thus,

$$\liminf_{t\to+\infty} P(t) \geq \lim_{t\to+\infty} \bar{P}_1(t) = \bar{P}_1^*.$$

Hence, there exists $T_3 > T_2$ such that for $t \geq T_3$,

$$P(t) > \bar{P}_1^* - \epsilon > 0.$$

By the second equation of (6), we have that for $t \geq T_3$,

$$\begin{aligned} \dot{P}(t) &\leq s_n(N^* + \epsilon) + r_pP(t) - \alpha(N^* - \epsilon)P(t) - \alpha P^2(t) - \alpha\beta(\bar{P}_1^* - \epsilon)P(t) \\ &\quad -\alpha G(\bar{P}_1^* - \epsilon)P(t) - c_1P(t) \\ &= -\alpha P^2(t) + [r_p - \alpha(N^* - \epsilon) - \alpha\beta(\bar{P}_1^* - \epsilon) - \alpha G(\bar{P}_1^* - \epsilon) - c_1]P(t) \\ &\quad +s_n(N^* + \epsilon) \\ &= -\alpha[P(t) - P_2^*][P(t) - Q_2^*], \end{aligned}$$

where P_2^* and Q_2^* are two equilibria of the following comparison system

$$\begin{cases} \dot{P}_2(t) = & -\alpha P_2^2(t) + [r_p - \alpha(N^* - \epsilon) - \alpha\beta(\bar{P}_1^* - \epsilon) - \alpha(\bar{P}_1^* - \epsilon) - c_1]P_2(t) \\ & +s_n(N^* + \epsilon), \\ P_2(T_3) = & P(T_3) > 0. \end{cases} \tag{21}$$

where $Q_2^* < 0$ and

$$\begin{aligned} P_2^* &= \frac{[r_p - \alpha(N^* - \epsilon) - \alpha\beta(\bar{P}_1^* - \epsilon) - \alpha G(\bar{P}_1^* - \epsilon) - c_1]}{2\alpha} \\ &\quad + \frac{\sqrt{[r_p - \alpha(N^* - \epsilon) - \alpha\beta(\bar{P}_1^* - \epsilon) - \alpha G(\bar{P}_1^* - \epsilon) - c_1]^2 + 4\alpha s_n(N^* + \epsilon)}}{2\alpha} \\ &> 0. \end{aligned}$$

Let

$$f(P_2) = -\alpha P_2^2 + [r_p - \alpha(N^* - \epsilon) - \alpha\beta(\bar{P}_1^* - \epsilon) - \alpha(\bar{P}_1^* - \epsilon) - c_1]P_2 + s_n(N^* + \epsilon).$$

Then, for sufficiently small $\epsilon > 0$,

$$f(P_2)\,|_{P_2=P_1^*} = -[\alpha(N^* - \epsilon) + \alpha\beta(P_1^* - \epsilon) + \alpha G(P_1^* - \epsilon) + c_1] < 0,$$

which shows that $P_2^* < P_1^*$. Furthermore, we also have

$$\limsup_{t\to+\infty} P(t) \leq \lim_{t\to+\infty} P_2(t) = P_2^*.$$

Hence, there exists $T_4 > T_3$ such that for $t \geq T_4$,

$$P(t) < P_2^* + \epsilon.$$

Again by the second equation of (6), for $t \geq T_4$,

$$\begin{aligned} \dot{P}(t) \quad &\geq \quad s_n(N^* - \epsilon) + r_p P(t) - \alpha(N^* + \epsilon)P(t) - \alpha P^2(t) - \alpha\beta(P_2^* + \epsilon)P(t) \\ &\quad -\alpha G(P_2^* + \epsilon)P(t) - c_1 P(t) \\ &= \quad -\alpha P^2(t) + [r_p - \alpha(N^* + \epsilon) - \alpha\beta(P_2^* + \epsilon) - \alpha G(P_2^* + \epsilon) - c_1]P(t) \\ &\quad +s_n(N^* - \epsilon) \\ &= \quad -\alpha[P(t) - \bar{P}_2^*][P(t) - \bar{Q}_2^*], \end{aligned}$$

where $\bar{P}_2^* > 0$ and $\bar{Q}_2^* < 0$ are two equilibria of the following comparison system

$$\begin{cases} \dot{\bar{P}}_2(t) = & -\alpha\bar{P}_2^2(t) + [r_p - \alpha(N^* + \epsilon) - \alpha\beta(P_2^* + \epsilon) - \alpha G(P_2^* + \epsilon) - c_1]\bar{P}_2(t) \\ & +s_n(N^* - \epsilon), \\ \bar{P}_2(T_4) = & P(T_4) > 0. \end{cases} \tag{22}$$

We also have that $\bar{P}_2^* > \bar{P}_1^*$ and

$$\liminf_{t\to+\infty} P(t) \geq \lim_{t\to+\infty} \bar{P}_2(t) = \bar{P}_2^*.$$

Repeating the above procedure, we have a time sequence $\{T_i\}$ and two other sequences $\{P_i^*\}$ and $\{\bar{P}_i^*\}$ such that $T_i < T_{i+1}$ and that

$$\begin{aligned} P_i^* \quad &= \quad \frac{[r_p - \alpha(N^* - \epsilon) - \alpha\beta(\bar{P}_{i-1}^* - \epsilon) - \alpha G(\bar{P}_{i-1}^* - \epsilon) - c_1]}{2\alpha} \\ &\quad + \frac{\sqrt{[r_p - \alpha(N^* - \epsilon) - \alpha\beta(\bar{P}_{i-1}^* - \epsilon) - \alpha G(\bar{P}_{i-1}^* - \epsilon) - c_1]^2 + 4\alpha s_n(N^* + \epsilon)}}{2\alpha} \\ &> \quad 0 \end{aligned}$$

and

$$\begin{aligned} \bar{P}_i^* \quad &= \quad \frac{[r_p - \alpha(N^* + \epsilon) - \alpha\beta(P_i^* + \epsilon) - \alpha G(P_i^* + \epsilon) - c_1]}{2\alpha} \\ &\quad + \frac{\sqrt{[r_p - \alpha(N^* + \epsilon) - \alpha\beta(P_i^* + \epsilon) - \alpha G(P_i^* + \epsilon) - c_1]^2 + 4\alpha s_n(N^* - \epsilon)}}{2\alpha} \\ &> \quad 0. \end{aligned}$$

where $\{P_i^*\}$ and $\{\bar{P}_i^*\}$ satisfy

$$\bar{P}_i^* \leq \bar{P}_{i+1}^* \leq \liminf_{t\to+\infty} P(t) \leq \limsup_{t\to+\infty} P(t) \leq P_{i+1}^* \leq P_i^*.$$

Let

$$\liminf_{i\to+\infty} P_i^* = A(\epsilon)$$

and

$$\liminf_{i\to+\infty} \bar{P}_i^* = B(\epsilon);$$

then we have

$$\begin{aligned} A(\epsilon) &= \frac{\{r_p - \alpha(N^* - \epsilon) - \alpha\beta[B(\epsilon) - \epsilon] - \alpha G[B(\epsilon) - \epsilon] - c_1\}}{2\alpha} + \\ &\quad \frac{\sqrt{\{r_p - \alpha(N^* - \epsilon) - \alpha\beta[B(\epsilon) - \epsilon] - \alpha G[B(\epsilon) - \epsilon] - c_1\}^2 + 4\alpha s_n(N^* + \epsilon)}}{2\alpha} \\ &> 0, \\ B(\epsilon) &= \frac{\{r_p - \alpha(N^* + \epsilon) - \alpha\beta[A(\epsilon) + \epsilon] - \alpha G[A(\epsilon) + \epsilon] - c_1\}}{2\alpha} + \\ &\quad \frac{\sqrt{\{r_p - \alpha(N^* + \epsilon) - \alpha\beta[A(\epsilon) + \epsilon] - \alpha G[A(\epsilon) + \epsilon] - c_1\}^2 + 4\alpha s_n(N^* - \epsilon)}}{2\alpha} \\ &> 0. \end{aligned}$$

Thus, we have

$$\begin{aligned} \alpha A(\epsilon)^2 - A(\epsilon)\{r_p - \alpha(N^* - \epsilon) - \alpha\beta[B(\epsilon) - \epsilon] - \alpha G[B(\epsilon) - \epsilon] - c_1\} = s_n(N^* + \epsilon), \\ \alpha B(\epsilon)^2 - B(\epsilon\{r_p - \alpha(N^* + \epsilon) - \alpha\beta[A(\epsilon) + \epsilon] - \alpha G[A(\epsilon) + \epsilon] - c_1\} = s_n(N^* - \epsilon), \end{aligned}$$

where $A = A(\epsilon)$ and $B = B(\epsilon)$ are both continuous respect to $\epsilon > 0$, and

$$A(\epsilon) \leq P^* \leq B(\epsilon)$$

for any sufficiently small $\epsilon > 0$.

Let $\epsilon \to 0$, so that

$$0 < A = A(0) \leq P^* \leq B = B(0)$$

and

$$\begin{cases} \alpha A^2 - A\{r_p - \alpha N^* - \alpha\beta B - \alpha GB - c_1\} = s_n N^*, \\ \alpha B^2 - B\{r_p - \alpha N^* - \alpha\beta A - \alpha GA - c_1\} = s_n N^*. \end{cases} \tag{23}$$

The first equation of (23) minus the second equation yields

$$\alpha(A + B)(A - B) - \delta(A - B) = 0, \tag{24}$$

where

$$\delta = r_p - \alpha N^* - c_1.$$

The first equation of (23) plus the second equation yields

$$\alpha(A^2 + B^2) - \delta(A + B) + 2\alpha G' AB = 2s_n N^*. \tag{25}$$

By (24), we have

$$A + B = \frac{\delta}{\alpha}, \text{ or } A - B = 0.$$

If $\delta > 0$ and $A + B = \delta/\alpha$ and we substitute it into (25), we have

$$\alpha[(\frac{\delta}{\alpha})^2 - 2AB] - \delta(\frac{\delta}{\alpha}) + 2\alpha G' AB = 2s_n N^*.$$

Hence,

$$\alpha(G' - 1)AB = s_n N^*.$$

If $G' > 1$, then

$$AB = \frac{s_n N^*}{\alpha(G' - 1)},$$

which means that A and B are two real roots of the equation

$$-\alpha(1 - G')X^2 + \delta(1 - G')X + s_n N^* = 0. \tag{26}$$

We have the following three cases.

1. If $\delta \leq 0$, it follows from $A + B = \delta/\alpha$ ($0 < A \leq P^* \leq B$) that we must have $A - B = 0$. Hence, $A = B = P^*$.

2. If $G' \leq 1$, it follows from $\alpha(G' - 1)AB = s_n N^* > 0$ that we must also have $A - B = 0$. Hence, $A = B = P^*$.

3. If $G' > 1$ and $\delta > 0$, let us define the functions

$$f(X) = -\alpha X^2 + \delta X + \frac{s_n N^*}{1 - G'},$$

and

$$g(X) = -\alpha X^2 + \frac{\delta}{1 + G'} X + \frac{s_n N^*}{1 + G'}.$$

Clearly,

$$f(A) = f(B) = 0, \; g(P^*) = 0.$$

We have the following three cases.

3a. If $\triangle = \delta^2 - 4\alpha \frac{s_n N^*}{G'-1} = 0$, the equation $f(X) = 0$ has two equal real roots $X^* = \delta/(2\alpha)$. Note that because $0 < A \leq P^* \leq B$, we must have $A = B = P^*$.

3b. If $\triangle < 0$, the equation $f(X) = 0$ has no real root, which shows that $A + B = \delta/\alpha$ is not true. Hence, $A = B = P^*$.

3c. If $\triangle > 0$, then $f(X) = 0$ has two different positive real roots $0 < X_1^* = A < X_2^* = B$.

From $g(P^*) = 0$, it is clear that

$$f(P^*) = -\frac{2\alpha G' P^*}{G' - 1}(P^* - \frac{\delta}{2\alpha}).$$

Hence, while $P^* < \delta/(2\alpha)$, it follows that

$$A < P^* < B.$$

If $P^* > \delta/(2\alpha)$, then $f(P^*) < 0$, which implies that $P^* < A$ or $P^* > B$. This is a contradiction to $A \leq P^* \leq B$. Hence, we have $A = B = P^*$.

If $P^* = \delta/(2\alpha)$, then it follows from $f(P^*) = 0$ that $P^* = A$ or $P^* = B$. On the other hand, we have from $f(X) = 0$ that

$$0 < X_1^* = A < \frac{\delta}{2\alpha} = P^* < X_2^* = B,$$

which is a contradiction to $P^* = A$ or $P^* = B$. Hence, it has $A = B = P^*$.

Therefore, we have the following.

Theorem 4. (i) *If $G' > 1$, $\delta > 0$ and $P^* < \delta/(2\alpha)$, then the system* (6) *is permanent for any time delays τ_1, τ_2, and τ_3.* (ii) *If $\delta \leq 0$, or $G' \leq 1$, or $G' > 1$, $\delta > 0$ and $P^* \geq \delta/(2\alpha)$, then the positive equilibrium (N^*, P^*) of* (6) *is globally asymptotically stable for any time delays τ_1, τ_2, and τ_3.*

6. **Discussion.** In this paper, we give an improved nonlinear delayed differential equation model, (2), of T cell development in the thymus based on some important experimental data. Then, by using the method of quasi-steady-state approximation, we reduce the higher-dimensional nonlinear delayed differential equation model into the two-dimensional nonlinear delayed differential equation (6). We also give a detailed analysis of the local and global asymptotic stability of the positive equilibrium (N^*, P^*) and permanence of (6). Theorem 3 shows that the positive equilibrium (N^*, P^*) is locally asymptotically stable for any time delays τ_1, τ_2, and τ_3. Theorem 4 gives a sufficient condition for global asymptotic stability of the positive equilibria (N^*, P^*). However, based on computer simulations, it is

strongly suggested that the conclusion "permanence" in (i) of Theorem 4 may be better stated as "globally asymptotically stable."

Acknowledgments. This research was partially supported by the Foundation of University of Science and Technology Beijing.

REFERENCES

[1] Z. Dou, Immunocyte and Diseases, Medical Scientific Press, Beijing, 2004.
[2] J. K. Hale, Theory of Functional Differential Equations, Springer-Verlag, New York, 1977.
[3] X. Jin and W. Ma, Stability analyse on a model of T Cell development in the thymus, Math. Practice and Theory, (2005), (in press).
[4] Y. Kuang, Delay Differential Equations with Applications in Population Dynamics, Academic Press, San Diego, 1993.
[5] V. Lakshmikantham and S. Leela, Differential and Integral Inequalities, Vol.I-II, Academic Press, New York, 1969.
[6] R. Mehr, A. Globerson and A. S. Perelson, Modeling positive and negative selection and differentiation processes in the thymus, J.Theory Biol., 175(1995), 103-126.
[7] R. Mehr, A. S. Perelson, M. Fridkis-Hareli and A. Globerson, Feedback regulation of T cell development in the hymus, J.Theory Biol., 181(1996), 157-167.
[8] W. E. Paul and Yuzhang Wu, The Foundation of Immunity, Science Press, Beijing, 2003.
[9] A. Qi, The Nonlinear Models of Immunity, Shanghai Scientific Press, Shanghai, 1998.
[10] Y. Qin, Y. Liu, L. Wang and Z. Zheng, The Stability of Dynamical Systems with Time Delays, Science Press, Beijing, 1989.

Received on February 17, 2005. Revised on May 3, 2005.

E-mail address: hongjing_shi@163.com
E-mail address: wanbiao_ma@sas.ustb.edu.cn (corresponding author)