Filomat 31:2 (2017), 347–361
DOI 10.2298/FIL1702347L

Published by Faculty of Sciences and Mathematics,
University of Niš, Serbia
Available at: http://www.pmf.ni.ac.rs/filomat

Global Stability Analysis of the Equilibrium of an Improved Time-Delayed Dynamic Model to Describe the Development of T Cells in the Thymus

Yang Li[a], Wanbiao Ma[a], Liming Xiao[b], Weitao Yang[b]

[a] *Department of Applied Mathematics, School of Mathematics and Physcis, University of Science and Technology Beijing, Beijing 100083, P. R. China*
[b] *School of Materials Science and Engineering, University of Science and Technology Beijing, Beijing 100083, P. R. China*

Abstract. In this paper, based on some biological meaning, triple-negative T cells (*TN*) and the immature single-positive T cells ($CD3^-4^+8^-$ and $CD3^-4^-8^+$) have been introduced into well known Mehr's nonlinear dynamic model which is used to describe proliferation, differentiation and death of T cells in the thymus (Modeling positive and negative selection and differentiation processes in the thymus, *Journal of Theoretical Biology*, 175 (1995) 103-126), and a class of improved nonlinear dynamic model with seven state variables and time delays has been proposed. Then, by using quasi-steady-state approximation and some classical analysis techniques of functional differential equations, the local and global stability of the equilibrium of the model have been analysed. Finally, some numerical simulations are given to summarize the applications of the theoretical results.

1. Introduction

T cells play an important role in cellular immunity. It is well known that T cells begin their development as precursor cells in the bone marrow. These cells migrate to the thymus, where they further divide, differentiate and develop into functional T cells. Finally, the T lymphocyte compartment includes two types of T cell sub-populations, characterized according to their functions and distinct cell membrane makers. Helper and inducer T cells (expressing the *CD*4 marker) regulate the function of the other immunocytes. Cytotoxic and suppressor T cells (expressing the *CD*8 maker) destroy virally infected cells and foreign transplants. The processes are complicated. Based on the data gained from experiments on mice by Finkel et al, Mehr et al proposed the following nonlinear dynamic model to describe proliferation, differentiation and death of T cells in the thymus [21, 22], for $t \geq 0$,

2010 *Mathematics Subject Classification*. Primary 34K20; Secondary 92B05
Keywords. T cell; Quasi-steady-state approximation; Time delay; Lyapunov functional; Global asymptotic stability.
Received: 11 November 2014; Accepted: 13 December 2015
Communicated by Jelena Manojlović
Corresponding author: Wanbiao Ma
Research partially supported by NNSF of China (11471034).
Email address: wanbiao_ma@ustb.edu.cn (Wanbiao Ma)

$$\begin{cases} \dot{N}(t) = (1 - \frac{N(t)}{K_n})[s + r_n N(t)] - (d_n + s_n)N(t), \\ \dot{P}(t) = s_n N(t) + (1 - \frac{Z}{K})r_p P(t) - (d_p + s_p)P(t), \\ \dot{P}_s(t) = s_p P(t) + (1 - \frac{Z}{K})r_{ps} P_s(t) - (d_{ps} + s_4 + s_8)P_s(t), \\ \dot{M}_4(t) = s_4 P_s(t) + (1 - \frac{Z}{K})r_4 M_4(t) - (d_4 + s_{04})M_4(t), \\ \dot{M}_8(t) = s_8 P_s(t) + (1 - \frac{Z}{K})r_8 M_8(t) - (d_8 + s_{08})M_8(t), \end{cases} \tag{1}$$

where N, P and P_s denote the numbers of the double negative (DN) cells, the double positive (DP) cells that are not sensitive to deletion and DP cells that are sensitive to deletion, respectively. M_4 represents the number of maturing single positive (SP, $CD4^+8^-$) cells, M_8 represents the number of maturing single positive (SP, $CD4^-8^+$) cells, and $Z = N + P + P_s + M_4 + M_8$ is the total thymic population.

The percentages of the cells in the various sub-populations are defined by

$$DN \equiv \frac{N}{Z}, \quad DP \equiv \frac{(P + P_s)}{Z}, \quad T_4 \equiv \frac{M_4}{Z}, \quad T_8 \equiv \frac{M_8}{Z}.$$

In each equation of the model (1), there is an input term that is the rate of entry of the cells from the previous compartment, except in the first equation, where we use s, the rate of seeding of T cell progenitor cells from the bone marrow. The parameters s_n, s_p, s_4 and s_8 represent maturation rates, that is, the rates of passage from one compartment to next. The parameters s_{04} and s_{08} represent the rates of export of mature T cells from the thymus. The parameters r_n, r_p, r_{ps}, r_4 and r_8 represent cell division rates, and the parameters d_n, d_p, d_{ps}, d_4 and d_8 represent the death rates, including the death of cells not rescued by positive selection and cell deletion due to negative selection.

Based on the analysis in [20–22], competition occurs during seeding and early development of thymocytes, hence, there is an upper bound for the DN cells, denoted here by K_n. Furthermore, due to the environmental restriction, there is also an upper bound for the total number of cells in thymus which is denoted by K. It is clear that competition in the model (1) is taken as the logistic form.

With the help of computer simulations, in [20, 21], it has been shown that the model (1) gives better estimates by experimental results for the total number of thymus cells and the fractions of various types of immature and mature thymocytes. In [10], by using stability theory of ordinary differential equations, detailed theoretical analysis of global asymptotic stability of the positive equilibrium of the model (1) has been given. Then, based on some important experimental date, in [27, 28], time delays are introduced into the model (1) and global dynamic properties of the positive equilibrium of the system has been analyzed by constructing suitable Liapunov functionals.

Precursor cells from bone marrow undergo the main intrathymic stages and develop into functional T cells. Finally, functional T cells emigrate to the periphery. A simplified diagram depicts the pathways of T cells differentiation in Figure 1(a). From [21], [26], [30], [34], it is has that T lymphocytes are generated in the thymus from bone-marrow (BM)-derived progenitor cells, which migrate to the thymus and settle in specific "niches" in the thymus stroma. This process is termed thymic seeding. Settled progenitors lack the cell surface markers of mature T cells, for example $CD3$, $CD4$ and $CD8$, hence are described as triple-negative (TN). Figure 1(b) depicts the progression in detail. In addition, mature single-positive T cells (SP, $CD4^+8^-$ and $CD4^-8^+$) are experienced the important process, immature single-positive T cells, which are prepared for differentiation in the junction of cortex and medulla (see, for example, [5], [14], [20], [22], [25], [29]).

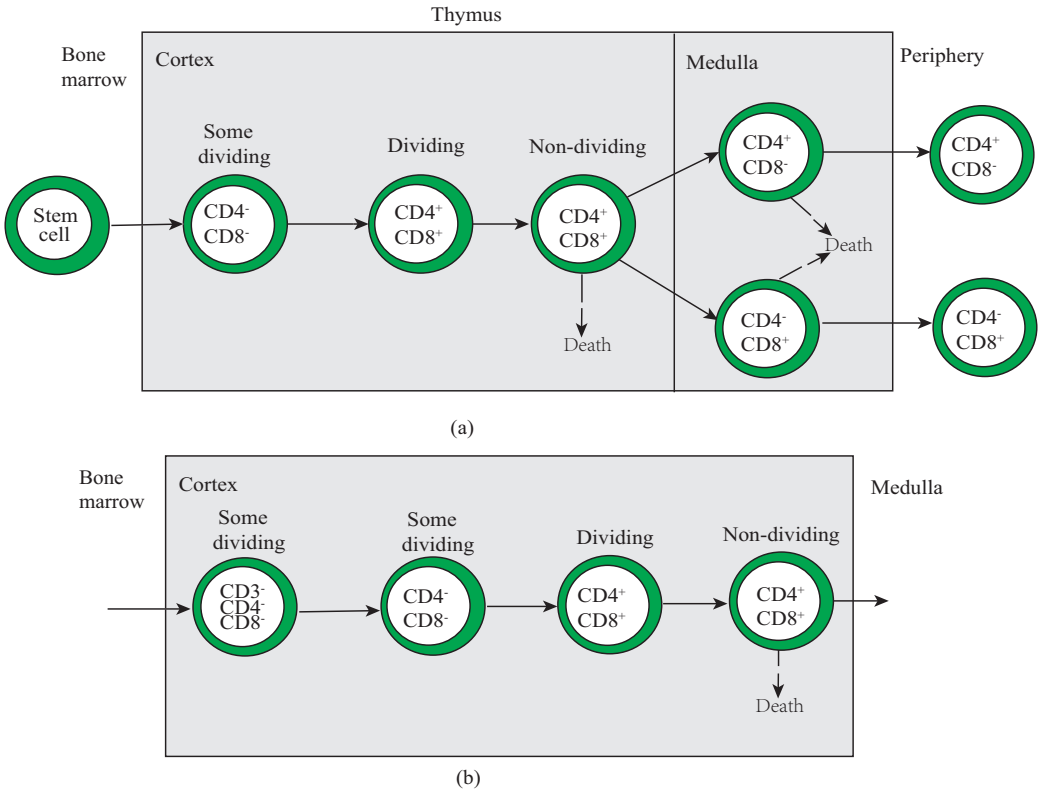

Figure 1: Pathways of T cell development.

The development of T cells in the thymus must go through positive and negative selection. The positive selection refers to double negative cells divide several times and subsequently express both the *CD*4 and *CD*8 markers, hence becoming double positive thymocytes. Depending on the affnity and the context of such binding, a developing *DP* thymocyte may be deleted (caused to die via apoptosis) or develop further into a $CD4^+8^-$ or $CD4^-8^+$ *SP* thymocyte. The latter subsets of thymocytes are the immediate precursors of mature $CD4^+8^-$ and $CD4^-8^+$ T cells. Negative selection is the deletion of self-reactive thymocytes, that is, thymocyte clones whose TCRs bind too strongly to self-antigens presented by self-MHC molecules. This prevents these cells from becoming auto-reactive and potentially harmful mature T cells. Cells without functional TCRs or cells with TCRs that cannot interact with self-MHC molecules appear to die in the thymus. Only the cells those who cannot identify the self-antigens complex can continue to develop mature $CD4^+8^-$ and $CD4^-8^+$ T cells (see, for example [21], [24], [26]).

Motivated by the model (1) and the biological arguments above, in the paper, triple-negative T cells (*TN*) and immature single-positive T cells, as two additional separated compartments, are introduced into the model (1), and it has the following revised dynamic model, for $t \geq 0$,

$$\begin{cases} \dot{T}_n(t) = (1 - \frac{T_n(t)}{L_n})[b_0 + rT_n(t)] - (d + s + s_r)T_n(t), \\ \dot{N}(t) = sT_n(t - \tau_1) + (1 - \frac{Z_n(t)}{K_n})[b_1 + r_nN(t)] - (d_n + s_n)N(t), \\ \dot{P}(t) = s_nN(t - \tau_2) + (1 - \frac{Z(t)}{K})r_pP(t) - (d_p + s_p)P(t), \\ \dot{P}_s(t) = s_pP(t - \tau_3) + (1 - \frac{Z(t)}{K})r_{ps}P_s(t) - (d_{ps} + s_m)P_s(t), \\ \dot{S}(t) = s_mP_s(t - \tau_4) + (1 - \frac{Z(t)}{K})r_sS(t) - (d_s + s_4 + s_8)S(t), \\ \dot{M}_4(t) = s_4S(t - \tau_5) + (1 - \frac{Z_2(t)}{K_2})r_4M_4(t) - (d_4 + s_{04})M_4(t), \\ \dot{M}_8(t) = s_8S(t - \tau_5) + (1 - \frac{Z_2(t)}{K_2})r_8M_8(t) - (d_8 + s_{08})M_8(t). \end{cases} \tag{2}$$

The biological meanings of all the state variables and the parameters in the model (2) are given as follows.
T_n: represents the number of *TN* cells;
N: represents the number of *DN* cells;
P: represents the number of *DP* cells that are not sensitive to deletion;
P_s: represents the number of *DP* cells that are sensitive to deletion;
S: represents the number of immature single-positive T cells;
M_4 and M_8: represent the numbers of maturing single positive $CD4^+8^-$ cells and $CD4^-8^+$ cells, respectively;
Z_n: represents the total number of *TN* cells and *DN* cells, $Z_n(t) \equiv T_n(t) + N(t)$;
L_n, K_n: represent upper bounds for the number of *TN* cells, and the total number of *TN* cells and *DN* cells in thymic cortex;
Z: represents the total thymic population in the thymic cortex, $Z(t) \equiv T_n(t) + N(t) + P(t) + P_s(t) + S(t)$;
K: represents an upper bound for the total number of cells in thymic cortex;
Z_2: represents the total number of $CD4^+8^-$ T cells and $CD4^-8^+$ T cells, $Z_2(t) \equiv M_4(t) + M_8(t)$;
K_2: represents an upper bound for the total number of $CD4^+8^-$ cells and $CD4^-8^+$ cells in thymic medulla;
$\tau_i (i = 1, 2, 3, 4, 5)$: represent the time delays. 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. In fact, from [3], it is has that the period of *DN* cells needs 14 days, *DP* cells needs 3 to 4 days, and *SP* cells needs 7 to 14 days. Hence, it is necessary to introduce time delays into the model (2).
b_0, b_1: represent the rate of seeding of T cell progenitor cells from the bone marrow;
r, r_n, r_p, r_{ps}, r_s, r_4 and r_8: represent cell division rates;
s, s_n, s_p, s_m, s_4 and s_8: represent the maturation rates, that is, the rates of passage from one compartment to next;
d, d_n, d_p, d_{ps}, d_s, d_4 and d_8: represent the death rates, including the death of cells not rescued by positive selection and cell deletion due to negative selection;
s_r: represents the rate of *TN* cells differentiation to other cells;
s_{04}, s_{08}: represent the rates of export of mature T cells from the thymus.

In biology, theoretical analysis on dynamic properties of the equilibrium of the model (2) is very important for a deep understanding of evolution mechanism of differentiation, development and maturation of T cells in thymus. This is main purpose of the paper.

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

$$\begin{cases} T_n(t) = \phi_1(t),\ N(t) = \phi_2(t),\ P(t) = \phi_3(t),\ P_s(t) = \phi_4(t), \\ S(t) = \phi_5(t),\ M_4(t) = \phi_6(t),\ M_8(t) = \phi_7(t)\ (-\Delta \le t \le 0]), \end{cases} \tag{3}$$

where the functions $\phi_i(t)(i = 1, 2, ..., 7)$ are continuous and positive on $[-\Delta, 0]$, $\Delta = \max\{\tau_i | i = 1, 2, \cdots, 5\}$.

With a standard argument (see, for example, [8] and [12]), it is easy to show that the solution $(T_n(t), N(t), P(t), P_s(t), S(t), M_4(t), M_8(t))$ of the model (2) with the initial condition (3) is existent, unique, positive and bounded on $[0, +\infty)$.

The organization of the paper is as follows.

In Section 2, by using quasi-steady-state approximation method (see, for example, [21, 22] and [24]), the model (2) with seven state variables is reduced to a system with three state variables. Then, in Section 3, by constructing suitable Liapunov functionals and using comparison principle, local and global stability of the equilibrium of the system with three state variables have been studied. Finally, in Section 4, some numerical simulations are given to summarize the applications of the results.

2. Quasi-Steady-State Approximation and Reduction of The Model

The model (2) is a nonlinear system with seven state variables. Usually, theoretical analysis on asymptotic properties of the model (2) is rather difficult. On the other hand, the simulations show that the time

evolution of the more mature thymocyte subsets (P_s, S, M_4, M_8) closely relate to that of P. Hence, it is possible to simplify the model (2) to a lower dimensional system by using quasi-steady-state approximation method as proposed in [21, 22] and [24].

Assume that

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

Furthermore, note that the parameter values given in [21, 22] and [24], it has that $Z_n \ll K_n$, $Z \ll K$, and $Z_2 \ll K_2$. Hence, it may further assume that $1 - Z/K \approx 1$ and $1 - Z_2/K_2 \approx 1$. It should be mentioned here that, from the simulations, these approximations are reasonable for all $t \in (\eta, \infty)$ for some small positive number η (see, for example, [21, 22] and [24], or the numerical simulations in Section 4). Therefore, it has from the model (2) that

$$\begin{cases} P_s(t) = \frac{s_p}{c_3 - r_{ps}} P(t - \tau_3), \\ S(t) = \frac{s_m s_p}{(c_4 - r_s)(c_3 - r_{ps})} P(t - \tau_3 - \tau_4), \\ M_4(t) = \frac{s_4 s_m s_p}{(c_5 - r_4)(c_4 - r_s)(c_3 - r_{ps})} P(t - \tau_3 - \tau_4 - \tau_5), \\ M_8(t) = \frac{s_8 s_m s_p}{(c_6 - r_8)(c_4 - r_s)(c_3 - r_{ps})} P(t - \tau_3 - \tau_4 - \tau_5), \end{cases} \tag{4}$$

where

$$c_0 = d + s + s_r > 0,\ c_1 = d_n + s_n > 0,\ c_2 = d_p + s_p > 0,\ c_3 = d_{ps} + s_m > 0,$$
$$c_4 = d_s + s_4 + s_8 > 0,\ c_5 = d_4 + s_{04} + h_4 > 0,\ c_6 = d_8 + s_{08} + h_8 > 0.$$

In the following discussions, it is further assumed that

$$c_3 - r_{ps} > 0, \quad c_4 - r_s > 0, \quad c_5 - r_4 > 0, \quad c_6 - r_8 > 0.$$

Let

$$c_0 = d + s + s_r > 0,\ c_1 = d_n + s_n > 0,\ c_2 = d_p + s_p > 0,$$
$$\alpha = \frac{r_p}{K},\ \beta = \frac{s_p}{c_3 - r_{ps}},\ \mu = \frac{s_m}{c_4 - r_s},\ \nu = \frac{1}{L_n},\ \gamma = \frac{1}{K_n}.$$

Hence, from the model (2) and (4), it has the following three-dimensional nonlinear delayed system for the state variables $T_n(t)$, $N(t)$ and $P(t)$, for $t \geq 0$,

$$\begin{cases} \dot{T}_n(t) = (1 - \nu T_n(t))[b_0 + rT_n(t)] - c_0 T_n(t), \\ \dot{N}(t) = sT_n(t - \tau_1) + (1 - \gamma Z_n(t))[b_1 + r_n N(t)] - c_1 N(t), \\ \dot{P}(t) = s_n N(t - \tau_2) + r_p P(t) - \alpha T_n(t) P(t) - \alpha N(t) P(t) - \alpha P^2(t) \\ \qquad -\alpha\beta P(t) P(t - \tau_3) - \alpha\beta\mu P(t) P(t - \tau_3 - \tau_4) - c_2 P(t). \end{cases} \tag{5}$$

In the following Section 3, detailed analysis on local and global stability of the equilibrium of the system (5) shall be given.

As usual, the initial condition of the system (5) is given as

$$T_n(t) = \phi_1(t),\ N(t) = \phi_2(t),\ P(t) = \phi_3(t)\ (-\varrho \leq t \leq 0), \tag{6}$$

where the functions $\phi_1(t)$, $\phi_2(t)$ and $\phi_3(t)$ are continuous and positive on $[-\varrho, 0]$, $\varrho = \max\{\tau_1, \tau_2, \tau_3 + \tau_4\}$.

It is also easily to show that the solution $(T_n(t), N(t), P(t))$ of the system (5) with the initial condition (6) is existent, unique, positive and bounded on $[0, +\infty)$.

3. Global Stability of the Equilibrium

In this section, let us first consider the existence of the positive equilibrium of the system (5).

Let (T_n, N, P) be any positive equilibrium of the system (5). Then, it has from the system (5) that

$$\begin{cases} (1 - \nu T_n)[b_0 + rT_n] - c_0 T_n = 0, \\ sT_n + (1 - \gamma Z_n)[b_1 + r_n N] - c_1 N = 0, \\ s_n N + r_p P - \alpha T_n P - \alpha N P - \alpha(1 + \beta + \beta\mu) P^2 - c_2 P = 0. \end{cases} \tag{7}$$

From the first equation of (7), it has that

$$T = T^* = \frac{r - \nu b_0 - c_0 + \sqrt{(r - \nu b_0 - c_0)^2 + 4\nu r b_0}}{2\nu r} > 0.$$

Hence, from the second equation of (7), it has that

$$-\gamma r_n N^2 + (r_n - \gamma b_1 - c_1 - \gamma r_n T^*)N + b_1 + (s - \gamma b_1)T^* = 0.$$

Therefore, it has that

$$N = N^* = \frac{B + \sqrt{B^2 + 4\gamma r_n C}}{2\gamma r_n} > 0,$$

if the following condition (H1) holds,

$$\text{(H1)} \quad C = b_1 + (s - \gamma b_1)T^* > 0, \quad \text{or} \quad C = 0 \quad \text{and} \quad B = r_n - \gamma b_1 - c_1 - \gamma r_n T^* > 0.$$

Similarly, it has from the third equation of (7) that

$$P = P^* = \frac{D + \sqrt{D^2 + 4\alpha s_n N^*(1 + \beta + \beta\mu)}}{2\alpha(1 + \beta + \beta\mu)} > 0,$$

where $D = r_p - \alpha T^* - \alpha N^* - c_2$.

In summary, it has from the discussions above that, if the condition (H1) holds, the system (5) has unique positive equilibrium (T^*, N^*, P^*).

For the local stability of the equilibrium (T^*, N^*, P^*), it easily has the following result.

Theorem 3.1. *The equilibrium (T^*, N^*, P^*) of the system (5) is locally asymptotically stable for any time delays τ_i $(i = 1, 2, 3, 4)$.*

The proof of Theorem 3.1 is similar to [27], and is omitted here.

Let us further consider global stability of the equilibrium (T^*, N^*, P^*) of the system (5).

First, it is noticed that the first equation of the system (5) only depends on the state variable $T_n(t)$. It has from known results that, T^* is unique positive equilibrium of the first equation of the system (5), and also globally asymptotically stable.

Since $\lim_{t\to+\infty} T_n(t) = T^*$, then, for any sufficiently small $\varepsilon > 0$, there exists some sufficiently large $t_0 > 0$ such that for $t \geq t_0$,

$$T^* - \varepsilon < T_n(t) < T^* + \varepsilon.$$

From the second equation of the system (5) and $N(t) \geq 0 (t \geq 0)$, it has that, for $t \geq t_0 + \varrho$,

$$\begin{aligned} \dot{N}(t) &= -\gamma r_n N^2(t) + (r_n - \gamma b_1 - c_1 - \gamma r_n T_n(t))N(t) + sT_n(t - \tau_1) - \gamma b_1 T_n(t) + b_1 \\ &\leq -\gamma r_n N^2(t) + [r_n - \gamma b_1 - c_1 - \gamma r_n(T^* - \varepsilon)]N(t) + s(T^* + \varepsilon) - \gamma b_1(T^* - \varepsilon) + b_1 \\ &= -\gamma r_n N^2(t) + (B + \gamma r_n \varepsilon)N(t) + C + (s + \gamma b_1)\varepsilon, \end{aligned}$$

and

$$\begin{aligned} \dot{N}(t) &= -\gamma r_n N^2(t) + (r_n - \gamma b_1 - c_1 - \gamma r_n T_n(t))N(t) + sT_n(t - \tau_1) - \gamma b_1 T_n(t) + b_1 \\ &\geq -\gamma r_n N^2(t) + [r_n - \gamma b_1 - c_1 - \gamma r_n(T^* + \varepsilon)]N(t) + s(T^* - \varepsilon) - \gamma b_1(T^* + \varepsilon) + b_1 \\ &= -\gamma r_n N^2(t) + (B - \gamma r_n \varepsilon)N(t) + C - (s + \gamma b_1)\varepsilon. \end{aligned}$$

By letting $\varepsilon \to 0$, it has the following comparison system,

$$\dot{U}(t) = -\gamma r_n U^2(t) + BU(t) + C. \tag{8}$$

The system (8) has unique positive equilibrium $U = N^*$ which is also globally asymptotically stable. Hence, it has from the comparison principle in [13] that

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

In the following, let us further show that $\lim_{t\to+\infty} P(t) = P^*$.

Again, for any sufficiently small $\varepsilon > 0$, there exists some $t_1 > t_0$ such that for $t \geq t_1$,

$$T^* - \varepsilon < T_n(t) < T^* + \varepsilon, \quad N^* - \varepsilon < N(t) < N^* + \varepsilon.$$

Therefore, it has from the third equation of the system (5) that, for $t \geq t_1 + \varrho$,

$$\begin{aligned}
\dot{P}(t) &= s_n N(t-\tau_2) + r_p P(t) - \alpha T_n(t)P(t) - \alpha N(t)P(t) - \alpha P^2(t) - \alpha\beta P(t)P(t-\tau_3) \\
&\quad -\alpha\beta\mu P(t)P(t-\tau_3-\tau_4) - c_2 P(t) \\
&\leq s_n(N^*+\varepsilon) + r_p P(t) - \alpha(T^*-\varepsilon)P(t) - \alpha(N^*-\varepsilon)P(t) - \alpha P^2(t) - \alpha\beta P(t)P(t-\tau_3) \\
&\quad -\alpha\beta\mu P(t)P(t-\tau_3-\tau_4) - c_2 P(t) \\
&= s_n(N^*+\varepsilon) + (D+2\alpha\varepsilon)P(t) - \alpha P^2(t) - \alpha\beta P(t)P(t-\tau_3) - \alpha\beta\mu P(t)P(t-\tau_3-\tau_4),
\end{aligned}$$

and

$$\begin{aligned}
\dot{P}(t) &= s_n N(t-\tau_2) + r_p P(t) - \alpha T_n(t)P(t) - \alpha N(t)P(t) - \alpha P^2(t) - \alpha\beta P(t)P(t-\tau_3) \\
&\quad -\alpha\beta\mu P(t)P(t-\tau_3-\tau_4) - c_2 P(t) \\
&\geq s_n(N^*-\varepsilon) + r_p P(t) - \alpha(T^*+\varepsilon)P(t) - \alpha(N^*+\varepsilon)P(t) - \alpha P^2(t) - \alpha\beta P(t)P(t-\tau_3) \\
&\quad -\alpha\beta\mu P(t)P(t-\tau_3-\tau_4) - c_2 P(t) \\
&= s_n(N^*-\varepsilon) + (D-2\alpha\varepsilon)P(t) - \alpha P^2(t) - \alpha\beta P(t)P(t-\tau_3) - \alpha\beta\mu P(t)P(t-\tau_3-\tau_4).
\end{aligned}$$

By letting $\varepsilon \to 0$, it has the following comparison system with time delays,

$$\dot{W}(t) = s_n N^* + DW(t) - \alpha W^2(t) - \alpha\beta W(t)W(t-\tau) - \alpha\beta\mu W(t)W(t-\sigma), \tag{9}$$

where $\tau = \tau_3$ and $\sigma = \tau_3 + \tau_4$.

It is clear that $W = P^*$ is unique positive equilibrium of the system (9). Let $W = W_1 < 0$ be another equilibrium of the system (9). It has the following results in [27, 28].

Lemma 3.2. *For the system (9), the following conclusions hold.*

Case (*i*) $D \leq 0$, *or* $\beta(1+\mu) \leq 1$, *or* $\beta(1+\mu) > 1$, $D > 0$ *and* $P^* \geq D/2\alpha$. *Then the equilibrium* P^* *of the system (9) is globally asymptotically stable for any time delays* τ_i $(i = 1, 2, 3, 4)$.

Case (*ii*) $\beta(1+\mu) > 1$, $D > 0$ *and* $P^* < D/2\alpha$. *Then the system (9) is permanent for any time delays* τ_i $(i = 1, 2, 3, 4)$, *and the following inequalities hold,*

$$N_0 \leq \liminf_{t\to+\infty} W(t) \leq P^* \leq \limsup_{t\to+\infty} W(t) \leq M_0,$$

where

$$N_0 = \frac{D[1-\beta(1+\mu)] + \sqrt{D^2[1-\beta(1+\mu)]^2 + 4\alpha s_n N^*[1-\beta(1+\mu)]}}{2\alpha[1-\beta(1+\mu)]},$$

$$M_0 = \frac{D[1-\beta(1+\mu)] - \sqrt{D^2[1-\beta(1+\mu)]^2 + 4\alpha s_n N^*[1-\beta(1+\mu)]}}{2\alpha[1-\beta(1+\mu)]}.$$

Let $(T_n(t), N(t), P(t))$ be any solution of the system (5). For Case (i), it has from Lemma 3.2 and the comparison theorem for functional differential equations in [13] that $\lim_{t\to+\infty} P(t) = P^*$.

For Case (ii), by using explicit bounds N_0 and M_0 for $\liminf_{t\to+\infty} W(t)$ and $\limsup_{t\to+\infty} W(t)$, respectively, in Lemma 3.2, it becomes possible to give sufficient conditions to ensure $\lim_{t\to+\infty} P(t) = P^*$ by constructing suitable Liapunov functionals.

The following result is main result of the paper.

Theorem 3.3. *For the system (5), the following conclusions hold.*

Case (i) $D \le 0$, *or* $\beta(1+\mu) \le 1$, *or* $\beta(1+\mu) > 1$, $D > 0$ *and* $P^* \ge D/2\alpha$. *Then the equilibrium* (T^*, N^*, P^*) *of the system (5) is globally asymptotically stable for any time delays* τ_i $(i = 1, 2, 3, 4)$.

Case (ii) $\beta(1+\mu) > 1$, $D > 0$ *and* $P^* < D/2\alpha$. *Then the equilibrium* (T^*, N^*, P^*) *of the system (5) is globally asymptotically stable, if the time delays* τ_3 *and* τ_4 *are small enough such that*

$$(1+\mu)\tau_3 + \mu\tau_4 \le (1+\mu+\frac{1}{\beta})\frac{1}{\alpha[(1+\beta+\beta\mu)(M_0-W_1)+2\beta(1+\mu)M_0]}. \tag{10}$$

Proof. For Case (i), it has from Lemma 3.2 that the equilibrium (T^*, N^*, P^*) of the system (5) is globally attractive for any time delays τ_i $(i = 1, 2, 3, 4)$. Hence, it has from Theorem 3.1 that the equilibrium (T^*, N^*, P^*) of the system (5) is globally asymptotically stable for any time delays τ_i $(i = 1, 2, 3, 4)$.

For Case (ii), it is only to show that $\lim_{t\to+\infty} W(t) = P^*$ holds.

For any $\varepsilon > 0$, there exists $t_2 > t_1$ such that, for any $t \ge t_2$,

$$0 < N_0 - \varepsilon < W(t) < M_0 + \varepsilon. \tag{11}$$

First, let us first consider a Lyapunov function as follows,

$$V_1 = W(t) - P^* - P^* \ln \frac{W(t)}{P^*}.$$

Calculating the derivative of V_1 along the solution of the system (9), it has that (see, for example, [2], [6, 7], [9], [11], [15], [19] and [23]), for $t \ge \sigma$,

$$\begin{aligned}
\dot{V}_1 &= \dot{W}(t) - \frac{P^*}{W(t)}\dot{W}(t) \\
&= s_nN^* + DW(t) - \alpha W^2(t) - \alpha\beta W(t)W(t-\tau) - \alpha\beta\mu W(t)W(t-\sigma) - s_nN^*\frac{P^*}{W(t)} - DP^* \\
&\quad +\alpha P^*W(t) + \alpha\beta P^*W(t-\tau) + \alpha\beta\mu P^*W(t-\sigma) \\
&= -\alpha[1+\beta(1+\mu)][W(t)-P^*]^2 + s_nN^*(2 - \frac{P^*}{W(t)} - \frac{W(t)}{P^*}) + \alpha\beta[W(t)-P^*][W(t)-W(t-\tau)] \\
&\quad +\alpha\beta\mu[W(t)-P^*][W(t)-W(t-\sigma)] \\
&= -\alpha[1+\beta(1+\mu)][W(t)-P^*]^2 + s_nN^*(2 - \frac{P^*}{W(t)} - \frac{W(t)}{P^*}) + \alpha\beta[W(t)-P^*]\int_{t-\tau}^{t}\dot{W}(\xi)d\xi \\
&\quad +\alpha\beta\mu[W(t)-P^*]\int_{t-\sigma}^{t}\dot{W}(\xi)d\xi.
\end{aligned}$$

Further, it has from the system (9) that, for $t \ge \sigma$,

$$\begin{aligned}
\dot{W}(t) &= s_nN^* + DW(t) - \alpha W^2(t) - \alpha\beta W(t)W(t-\tau) - \alpha\beta\mu W(t)W(t-\sigma) \\
&= s_nN^* + DW(t) - \alpha[1+\beta(1+\mu)]W^2(t) + \alpha\beta W(t)\int_{t-\tau}^{t}\dot{W}(\xi)d\xi + \alpha\beta\mu W(t)\int_{t-\sigma}^{t}\dot{W}(\xi)d\xi \\
&= -\alpha[1+\beta(1+\mu)][W(t)-W_1][W(t)-P^*] + \alpha\beta W(t)\int_{t-\tau}^{t}\dot{W}(\xi)d\xi + \alpha\beta\mu W(t)\int_{t-\sigma}^{t}\dot{W}(\xi)d\xi \\
&= -\alpha[1+\beta(1+\mu)][W(t)-W_1][W(t)-P^*] - \alpha\beta W(t)[W(t-\tau)-P^*] + \alpha\beta W(t)[W(t)-P^*] \\
&\quad -\alpha\beta\mu W(t)[W(t-\sigma)-P^*] + \alpha\beta\mu W(t)[W(t)-P^*].
\end{aligned}$$

Hence, it has that, for $t \geq \sigma$,

$$\begin{aligned} |\dot{W}(t)| \leq\ & \alpha[1+\beta(1+\mu)](M_0+\varepsilon-W_1)|W(t)-P^*| + \alpha\beta(M_0+\varepsilon)|W(t-\tau)-P^*| \\ & +\alpha\beta(M_0+\varepsilon)|W(t)-P^*| + \alpha\beta\mu(M_0+\varepsilon)|W(t-\sigma)-P^*| + \alpha\beta\mu(M_0+\varepsilon)|W(t)-P^*|. \end{aligned} \tag{12}$$

By (12), it also has that, for $t \geq t_2 + \sigma$,

$$\begin{aligned} \alpha\beta[W(t)-P^*]\int_{t-\tau}^{t}\dot{W}(\xi)d\xi \leq\ & \alpha\beta\int_{t-\tau}^{t}|W(t)-P^*||\dot{W}(\xi)|d\xi \\ \leq\ & \frac{1}{2}\alpha^2\beta[1+\beta(1+\mu)](M_0+\varepsilon-W_1)\int_{t-\tau}^{t}([W(t)-P^*]^2+[W(\xi)-P^*]^2)d\xi \\ & +\frac{1}{2}\alpha^2\beta^2(M_0+\varepsilon)\int_{t-\tau}^{t}([W(t)-P^*]^2+[W(\xi-\tau)-P^*]^2)d\xi \\ & +\frac{1}{2}\alpha^2\beta^2(M_0+\varepsilon)\int_{t-\tau}^{t}([W(t)-P^*]^2+[W(\xi)-P^*]^2)d\xi \\ & +\frac{1}{2}\alpha^2\beta^2\mu(M_0+\varepsilon)\int_{t-\tau}^{t}([W(t)-P^*]^2+[W(\xi-\sigma)-P^*]^2)d\xi \\ & +\frac{1}{2}\alpha^2\beta^2\mu(M_0+\varepsilon)\int_{t-\tau}^{t}([W(t)-P^*]^2+[W(\xi)-P^*]^2)d\xi \\ =\ & \frac{1}{2}\mu_1\tau[W(t)-P^*]^2+\frac{1}{2}\theta_1\int_{t-\tau}^{t}[W(\xi)-P^*]^2d\xi \\ & +\frac{1}{2}\alpha^2\beta^2(M_0+\varepsilon)\int_{t-\tau}^{t}[W(\xi-\tau)-P^*]^2d\xi \\ & +\frac{1}{2}\alpha^2\beta^2\mu(M_0+\varepsilon)\int_{t-\tau}^{t}[W(\xi-\sigma)-P^*]^2d\xi, \end{aligned}$$

where

$$\mu_1 = \mu_1(\varepsilon) = \alpha^2\beta\{[1+\beta(1+\mu)](M_0+\varepsilon-W_1)+2\beta(1+\mu)(M_0+\varepsilon)\},$$

$$\theta_1 = \theta_1(\varepsilon) = \alpha^2\beta\{[1+\beta(1+\mu)](M_0+\varepsilon-W_1)+\beta(1+\mu)(M_0+\varepsilon)\}.$$

Similarly, it has that, for $t \geq t_2 + \sigma$,

$$\begin{aligned} \alpha\beta\mu[W(t)-P^*]\int_{t-\sigma}^{t}\dot{W}(\xi)d\xi \leq\ & \frac{1}{2}\mu_2\sigma[W(t)-P^*]^2+\frac{1}{2}\theta_2\int_{t-\sigma}^{t}[W(\xi)-P^*]^2d\xi \\ & +\frac{1}{2}\alpha^2\beta^2\mu(M_0+\varepsilon)\int_{t-\sigma}^{t}[W(\xi-\tau)-P^*]^2d\xi \\ & +\frac{1}{2}\alpha^2\beta^2\mu^2(M_0+\varepsilon)\int_{t-\sigma}^{t}[W(\xi-\sigma)-P^*]^2d\xi, \end{aligned}$$

where

$$\mu_2 = \mu_2(\varepsilon) = \mu\mu_1(\varepsilon), \quad \theta_2 = \theta_2(\varepsilon) = \mu\theta_1(\varepsilon).$$

Hence, it has that, for $t \geq t_2 + \sigma$,

$$\begin{aligned}
\dot{V}_1 \leq\ & -\alpha[1+\beta(1+\mu)][W(t)-P^*]^2 + s_n N^*\left(2 - \frac{P^*}{W(t)} - \frac{W(t)}{P^*}\right) \\
& + \frac{1}{2}\mu_1\tau[W(t)-P^*]^2 + \frac{1}{2}\theta_1\int_{t-\tau}^{t}[W(\xi)-P^*]^2 d\xi + \frac{1}{2}\alpha^2\beta^2(M_0+\varepsilon)\int_{t-\tau}^{t}[W(\xi-\tau)-P^*]^2 d\xi \\
& + \frac{1}{2}\alpha^2\beta^2\mu(M_0+\varepsilon)\int_{t-\tau}^{t}[W(\xi-\sigma)-P^*]^2 d\xi \\
& + \frac{1}{2}\mu_2\sigma[W(t)-P^*]^2 + \frac{1}{2}\theta_2\int_{t-\sigma}^{t}[W(\xi)-P^*]^2 d\xi + \frac{1}{2}\alpha^2\beta^2\mu(M_0+\varepsilon)\int_{t-\sigma}^{t}[W(\xi-\tau)-P^*]^2 d\xi \\
& + \frac{1}{2}\alpha^2\beta^2\mu^2(M_0+\varepsilon)\int_{t-\sigma}^{t}[W(\xi-\sigma)-P^*]^2 d\xi.
\end{aligned}$$

Next, motivated by the methods in [1], [4], [16–18], [28], [31–33], and [35], let us define a series of differentiable functionals $V_i (i = 2, 3, 4, 5, 6, 7)$, and then consider their derivatives along the solutions of the system (9), for $t \geq t_2 + \sigma$,

$$\begin{aligned}
V_2 &= \frac{1}{2}\theta_1\int_{t-\tau}^{t}\int_{\theta}^{t}[W(\xi)-P^*]^2 d\xi d\theta, \\
\dot{V}_2 &= \frac{1}{2}\theta_1\tau[W(t)-P^*]^2 - \frac{1}{2}\theta_1\int_{t-\tau}^{t}[W(\xi)-P^*]^2 d\xi, \\
V_3 &= \frac{1}{2}\alpha^2\beta^2(M_0+\varepsilon)\left\{\int_{t-\tau}^{t}\int_{\theta}^{t}[W(\xi-\tau)-P^*]^2 d\xi d\theta + \tau\int_{t-\tau}^{t}[W(\xi)-P^*]^2 d\xi\right\}, \\
\dot{V}_3 &= \frac{1}{2}\alpha^2\beta^2(M_0+\varepsilon)\tau[W(t)-P^*]^2 - \frac{1}{2}\alpha^2\beta^2(M_0+\varepsilon)\int_{t-\tau}^{t}[W(\xi-\tau)-P^*]^2 d\xi, \\
V_4 &= \frac{1}{2}\alpha^2\beta^2\mu(M_0+\varepsilon)\left\{\int_{t-\tau}^{t}\int_{\theta}^{t}[W(\xi-\sigma)-P^*]^2 d\xi d\theta + \tau\int_{t-\sigma}^{t}[W(\xi)-P^*]^2 d\xi\right\}, \\
\dot{V}_4 &= \frac{1}{2}\alpha^2\beta^2\mu(M_0+\varepsilon)\tau[W(t)-P^*]^2 - \frac{1}{2}\alpha^2\beta^2\mu(M_0+\varepsilon)\int_{t-\tau}^{t}[W(\xi-\sigma)-P^*]^2 d\xi, \\
V_5 &= \frac{1}{2}\theta_2\int_{t-\sigma}^{t}\int_{\theta}^{t}[W(\xi)-P^*]^2 d\xi d\theta, \\
\dot{V}_5 &= \frac{1}{2}\theta_2\sigma[W(t)-P^*]^2 - \frac{1}{2}\theta_2\int_{t-\sigma}^{t}[W(\xi)-P^*]^2 d\xi,
\end{aligned}$$

$$\begin{aligned}
V_6 &= \frac{1}{2}\alpha^2\beta^2\mu(M_0+\varepsilon)\left\{\int_{t-\sigma}^{t}\int_{\theta}^{t}[W(\xi-\tau)-P^*]^2 d\xi d\theta + \sigma\int_{t-\tau}^{t}[W(\xi)-P^*]^2 d\xi\right\}, \\
\dot{V}_6 &= \frac{1}{2}\alpha^2\beta^2\mu(M_0+\varepsilon)\sigma[W(t)-P^*]^2 - \frac{1}{2}\alpha^2\beta^2\mu(M_0+\varepsilon)\int_{t-\sigma}^{t}[W(\xi-\tau)-P^*]^2 d\xi, \\
V_7 &= \frac{1}{2}\alpha^2\beta^2\mu^2(M_0+\varepsilon)\left\{\int_{t-\sigma}^{t}\int_{\theta}^{t}[W(\xi-\sigma)-P^*]^2 d\xi d\theta + \sigma\int_{t-\sigma}^{t}[W(\xi)-P^*]^2 d\xi\right\}, \\
\dot{V}_7 &= \frac{1}{2}\alpha^2\beta^2\mu^2(M_0+\varepsilon)\sigma[W(t)-P^*]^2 - \frac{1}{2}\alpha^2\beta^2\mu^2(M_0+\varepsilon)\int_{t-\sigma}^{t}[W(\xi-\sigma)-P^*]^2 d\xi.
\end{aligned}$$

Now, define the following Lyapunov functional,

$$V = \sum_{i=1}^{7} V_i.$$

Then, along the solutions of the system (9), it has that, for $t \geq t_2 + \sigma$,

$$\dot{V} \leq M[W(t) - P^*]^2 + s_n N^*(2 - \frac{P^*}{W(t)} - \frac{W(t)}{P^*}) \leq M[W(t) - P^*]^2,$$

where

$$\begin{aligned} M = M(\varepsilon) = & -\alpha[1 + \beta(1 + \mu)] + \frac{1}{2}\mu_1\tau + \frac{1}{2}\mu_2\sigma + \frac{1}{2}\theta_1\tau + \frac{1}{2}\theta_2\sigma + \frac{1}{2}\alpha^2\beta^2(M_0 + \varepsilon)\tau \\ & + \frac{1}{2}\alpha^2\beta^2\mu(M_0 + \varepsilon)\tau + \frac{1}{2}\alpha^2\beta^2\mu(M_0 + \varepsilon)\sigma + \frac{1}{2}\alpha^2\beta^2\mu^2(M_0 + \varepsilon)\sigma. \end{aligned}$$

Since the condition (10) of Theorem 3.3 is equivalent to $M = M(0) < 0$, hence, for sufficiently small $\varepsilon > 0$, it has that $M = M(\varepsilon) < 0$. Therefore, it has that, for $t \geq t_2 + \sigma$,

$$\dot{V}(t) \leq M[W(t) - P^*]^2 \leq 0.$$

Integrating the above inequality from $t_2 + \sigma$ to t yields that, for $t \geq t_2 + \sigma$,

$$V(t) + \int_{t_2+\sigma}^{t} [W(u) - P^*]^2 du \leq V(t_2 + \sigma) = \text{const.}.$$

Clearly, the above inequality implies that the function $|W(t) - P^*|$ is bounded for $t \geq 0$, and that $\int_{t_2+\sigma}^{+\infty} [W(t) - P^*]^2 dt < +\infty$. Therefore, it has from Barbălat lemma that $\lim_{t\to+\infty} W(t) = P^*$.

This completes the proof of Theorem 3.3. □

4. Numerical Simulations

In Section 3, the sufficient conditions for global stability of the equilibrium (T^*, N^*, P^*) of the system (5) are given. In this section, let us give some numerical simulations to summarize the applications of Theorem 3.3.

The parameters in Table 1 below are taken from [21, 22]. Then, it has that

$$T^* = 71.3703, \quad N^* = 1.8197 \times 10^6, \quad P^* = 1.0266 \times 10^7, \quad C = 171.3698,$$

$$D = 0.3727, \quad \beta(1 + \mu) = 2.5715, \quad \frac{D}{2\alpha} = 1.2423 \times 10^7.$$

Clearly, the condition (H1) holds since $C > 0$. Furthermore, the conditions of Case (ii) in Theorem 3.3, $D > 0, \beta(1 + \mu) > 1$ and $P^* < D/2\alpha$, are also satisfied. The condition (10) becomes

$$f(\tau_3, \tau_4) = 1.8\tau_3 + 0.8\tau_4 < 0.8477. \tag{13}$$

Let us choose the initial functions as $\varphi_i(t) = 4$ for $t \in [-\tau, 0]$, and time delays $\tau_1 = \tau_2 = \tau_5 = 1$. Figure 2 shows that the curves of the solutions of the system (5) converge to the equilibrium (T^*, N^*, P^*) as $t \to +\infty$ when $\tau_3 = 0.2, \tau_4 = 0.5, f(\tau_3, \tau_4) = 0.76 < 0.8477$.

Table 1: Standard kinetic parameters for the model (2)

$b_0 = 100$	$r = 0.2$	$d = d_n = 0$	$s = 1.0$
$b_1 = 100$	$r_n = 1.1$	$d_p = 0.6$	$s_n = 1.0$
$s_{04} = 0.4$	$r_p = 1.5$	$d_{ps} = 0.95$	$s_p = 0.5$
$s_{08} = 0.4$	$r_{ps} = 1.0$	$d_s = 0.2$	$s_m = 0.4$
$L_n = 10^5$	$r_s = 0.1$	$d_4 + t_4 = 0.6$	$s_r = 0.6$
$K_n = 2 \times 10^7$	$r_4 = 0.02$	$d_8 + t_8 = 0.6$	$s_4 = 0.3$
$K = 10^8$	$K_2 = 10^7$	$r_8 = 0.02$	$s_8 = 0.1$

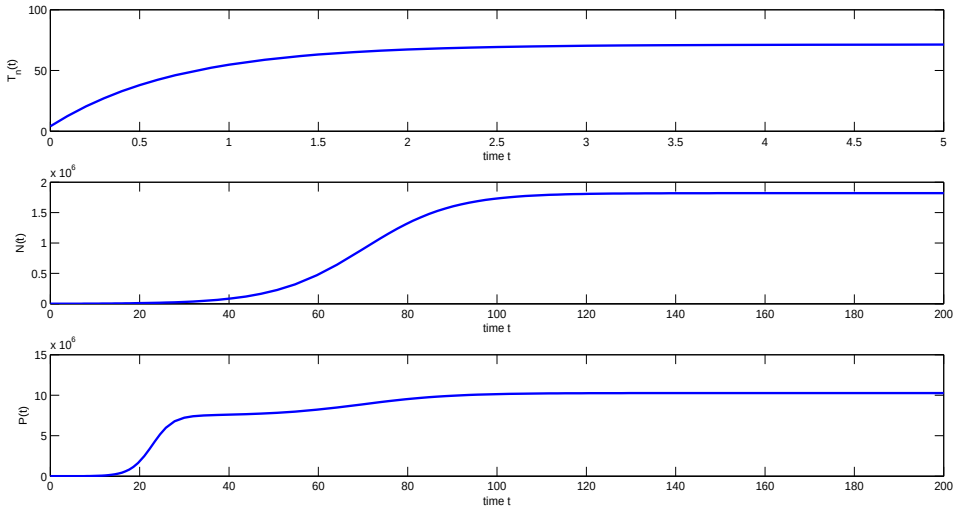

Figure 2: Representative simulations of the system (5) with $\tau_3 = 0.2, \tau_4 = 0.5, f(\tau_3, \tau_4) = 0.76 < 0.8477$.

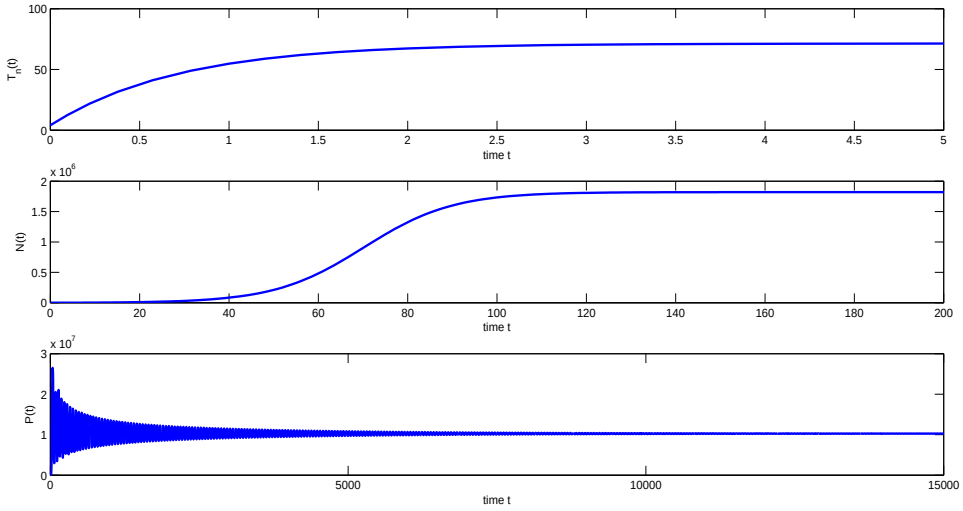

Figure 3: Representative simulations of the system (5) with $\tau_3 = 25, \tau_4 = 66, f(\tau_3, \tau_4) = 97.8 > 0.8477$.

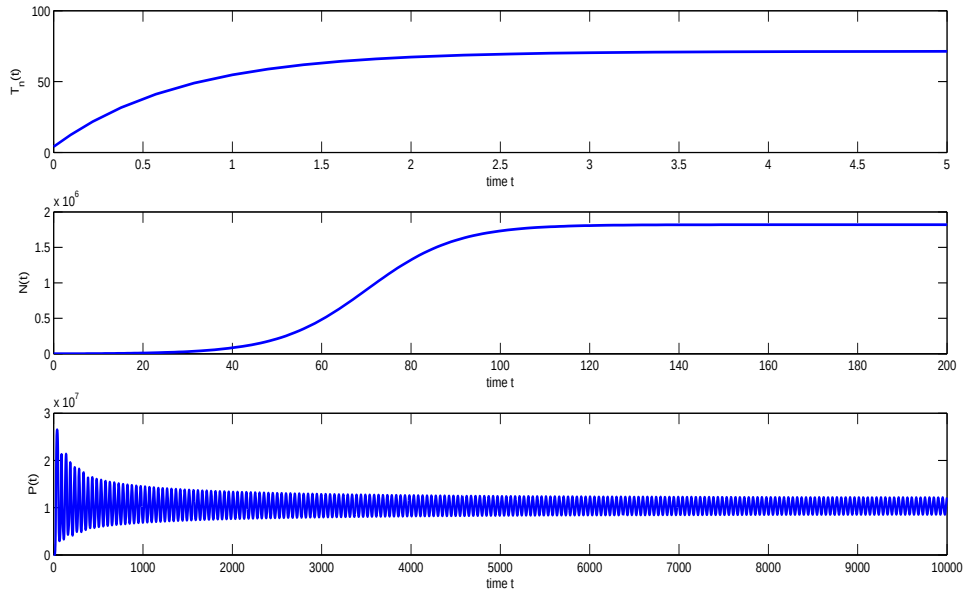

Figure 4: Representative simulations of the system (5) with $\tau_3 = 25, \tau_4 = 67, f(\tau_3, \tau_4) = 98.6 > 0.8477$.

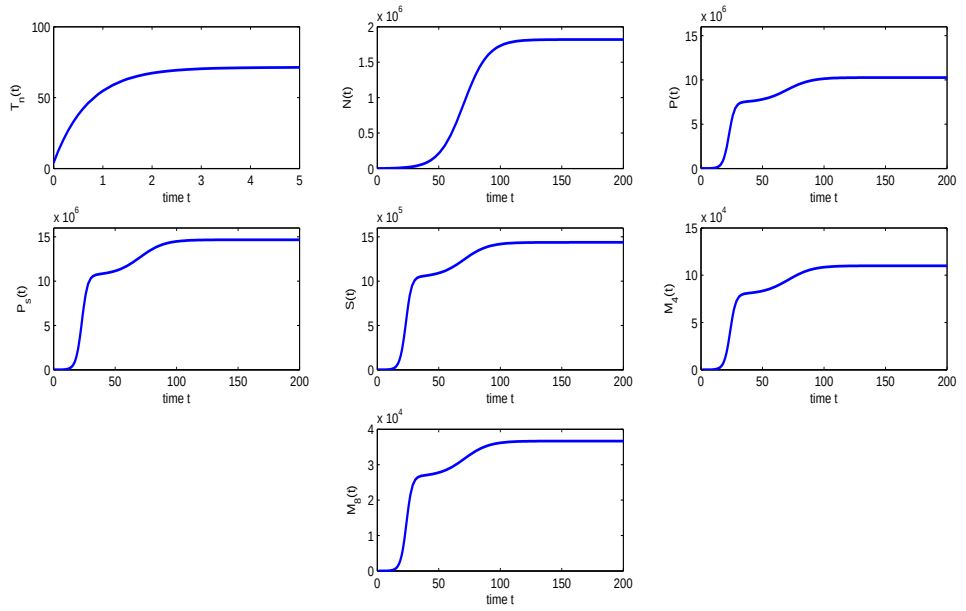

Figure 5: Representative simulations of the system (5) with $\tau_3 = 0.2, \tau_4 = 0.5, f(\tau_3, \tau_4) = 0.76 < 0.8477$ and the quasi-steady-state approximations (4).

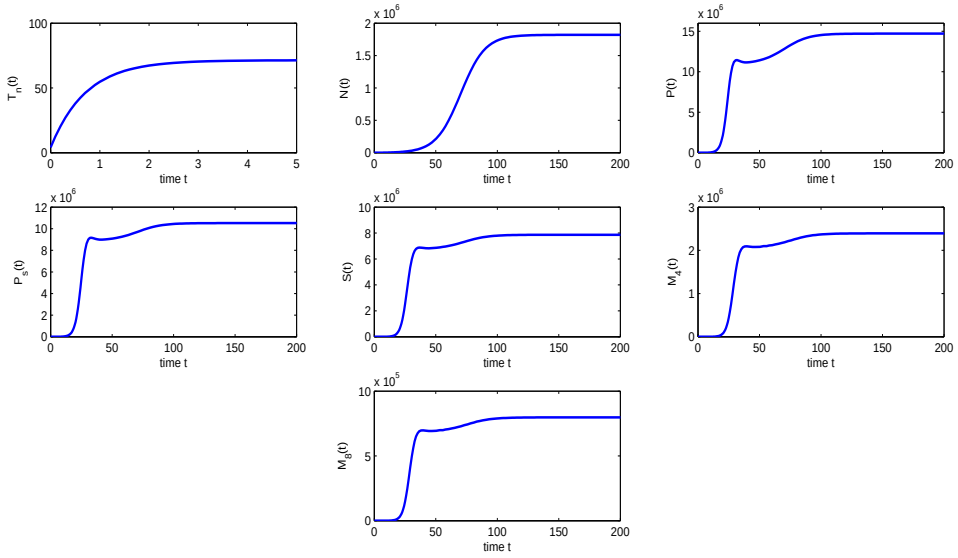

Figure 6: Representative simulations of the full model (2) with $\tau_3 = 0.2, \tau_4 = 0.5, f(\tau_3, \tau_4) = 0.76 < 0.8477$.

Furthermore, Figures 3-4 show that the curves of the solutions of the system (5) still converge to the equilibrium (T^*, N^*, P^*) as $t \to +\infty$ when $\tau_3 = 25, \tau_4 = 66, f(\tau_3, \tau_4) = 97.8 > 0.8477$, and that the curves of the solutions of the system (5) will become oscillated and do not converge to the equilibrium (T^*, N^*, P^*) as $t \to +\infty$ when $\tau_3 = 25, \tau_4 = 67, f(\tau_3, \tau_4) = 98.6 > 0.8477$. Hence, the condition (10) in Theorem 3.3 still has enough space to be improved.

Comparing Figure 5 with Figure 6, it is found that the system (5) captures dynamic behaviors of the full model (2), though steady-state values for all thymic subsets except $T_n(t)$ and $N(t)$ may be slightly different. It is also seen that the quasi-steady-state approximation is valid, and that thymic sub-populations show similar asymptotic properties in mathematics (see, for example, [21] and [24]).

5. Conclusions

It is well known that T cells have important effects on regulating the stability of the environment in human body. In this paper, an improved nonlinear delayed dynamic model (2) at cellular level is given to describe the proliferation, differentiation and death of T cells in the thymus. In biology, theoretical analysis on dynamic properties of the equilibrium of the model (2) is very important for a deep understanding of the evolution mechanism of the proliferation, differentiation and maturation of T cells in the thymus.

Based on the method of quasi-steady-state approximation, the model (2) with seven state variables is reduced to the system (5) with three state variables. The system (5) exists a unique positive equilibrium (T^*, N^*, P^*) under the condition (H1). The main result of this paper is Theorem 3.3 which gives sufficient conditions for global stability of the equilibrium (T^*, N^*, P^*) of the system (5). In biology, global stability of the equilibrium (T^*, N^*, P^*) means that, as the time t increases and tends to infinity, the numbers of TN cells, DN cells and DP cells shall tend to the constant values T^*, N^* and P^*, respectively. For the Case (i) in Theorem 3.3, it is seen that the time delays τ_3 and τ_4 are *harmless* for global stability of the equilibrium (T^*, N^*, P^*). For the Case (ii) in Theorem 3.3, it is seen that the time delays τ_3 and τ_4 have effects on global stability of the equilibrium (T^*, N^*, P^*). Notice the biological meanings of the parameters in the full model (2) and the numerical simulations in Section 4, it has that the sufficient conditions in Theorem 3.3 for global stability of the equilibrium (T^*, N^*, P^*) of the system (5) are reasonable.

Acknowledgments

The authors are grateful to the editor and anonymous reviewers for their valuable comments and suggestions to improve the quality of the paper.

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