Discrete and Continuous Dynamical Systems - Series B
Vol. 28, No. 7, July 2023, pp. 3925-3954
doi:10.3934/dcdsb.2022248

ON THE THREE DIMENSIONAL COMPETITION SYSTEMS ARISING FROM ARABIDOPSIS CLOCK

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(Communicated by Xiao-Qiang Zhao)

Abstract. In this paper, we study mathematical models of three dimensional competitive systems originated from the repressillator and their variants. There are two parts for the mathematical results. In part I, we first prove the uniqueness of the positive equilibrium (x^*, y^*, z^*). Then we present necessary and sufficient conditions for their local asymptotic stability and instability. In part II, we present sufficient conditions for the global asymptotic stability of (x^*, y^*, z^*) provided (x^*, y^*, z^*) is locally asymptotic stable.

1. **Introduction.** Periodic oscillation is an important form of dynamics. The fundamental and simple harmonic oscillator serves as a classic example of linear oscillators. However, the stability of linear oscillator can be easily changed with a nonlinear perturbation. The well-known Hopf bifurcation as the generation of periodic orbits has been a core element in nonlinear dynamics for oscillations [7]. Periodic oscillation is a vital element for functional dynamics in biology. With a network of biochemical regulation, the levels of components in a cell or an organism can oscillate periodically, which allows the cell to "count" time and to entrain the cell differentiation process with developmental stages [24, 19]. With these innate clocks, cells predict and prepare for the time-dependent events by signaling the cell, where gene expression[30, 31] or other biochemical events such as cell cycles[2, 9, 22], circadian clocks [25, 26, 29] and somite formation [16, 21], among others are taking place in the right time orders.

In viewing cells as tiny biochemical reactors, the uncertainty and heterogeneity in the biochemical regulations has been an important aspect of study, a phenomenon that is often called "noise"[5]. While noise can be taken as an advantageous addition to the system[4], in many cases, it is necessary to cope with such uncertainties to maintain many functions. In coping with such noises, a faithful and robust oscillator

2020 *Mathematics Subject Classification.* 35K57, 92D25.
Key words and phrases. Repressilator; transcriptional control; post-translational control; Hill function of repressive process; Hill function of activating process; positive feedback; three-dimensional competitive system; Poincaré-Bendixson Theorem; global stability of positive equilibrium; limit cycle; orbital stability of periodic orbit; second compound matrix.

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is often required. It has been reported that oscillators gain robustness through the coupling with dual negative feedback[18, 28], interlinking a negative feedback with a positive feedback[3, 8, 14], or incoherent feed-forward loops [14].

An artificially synthesized oscillator in *E. coli* cells, the repressillator[6], has drawn much attention. It was shown that tiny *E. coli* cells with this very simple 3-gene network can produce oscillation in reporter fluorescence protein, but such oscillations are not robust, as a cell can cease to oscillate, and the phase of oscillation was not kept well. While an improved version of repressillator is reported years afterwards[23], various mechanisms are also known to keep oscillations robust[1]. For example, a positive feedback provides the system offers a tunability in the oscillation frequency but maintains the amplitude [32]. Positive feedback loops facilitate hysteric two-state building, while feed-ford structure allows a faster switch in circadian clocks. [14] It was also shown that such a repressillator circuit cannot oscillate properly if the genes are leaky in their transcriptional regulation, and a translational control, such as protein degradation or activation/deactivation, is important to keep the oscillation[15]. The repressillator as a classic and almost the simplest biological oscillator has been a very suitable object for theoretical and computational studies.

In this paper we shall study the three-dimensional competition systems deriving from repressillator. Especially we analyze the mathematical models of $M1 - M5$ in [15] in which the authors investigate the roles of each transcriptional and post-translational regulations and their combination of these two regulations. Their results provide insights into the plausible importance in coupling transcription and post-translation control in the clock system.

Fortunately these three-dimensional systems are competition systems of special types. M.Hirsch [10] in 1980 proved the Poincaré-Bendixson Theorem for three dimensional competition systems. We apply Poincaré-Bendixson Theorem directly to show that the solution either tends to a unique locally stable equilibrium or tends to a limit cycle. Further more we apply the second compound method introduced by Muldoney [20] to prove that for the models $M1$-$M5$ under some conditions every periodic orbit, whenever it exists, is orbitally asymptotically stable. Thus we can show that if the unique equilibrium is locally asymptotically stable, then it is globally asymptotically stable. However, if the limit cycle exists then it is orbitally asymptotically stable. But we are unable to prove that the limit cycle is unique.

In Section 2 we state the Models $M1 - M5$ in [15]. The main results for the Models $M1 - M5$ are presented in Section 3. Section 4 is the section of numerical test results and discussion. We deferred the proofs of Theorem 3.1 to Theorem 3.5 to the Section 5.

2. **The Models.**

Let $h_i(w) = \dfrac{\kappa_i^{n_i}}{\kappa_i^{n_i} + w^{n_i}}$ represent Hill function of repressive process and $g_i(w) = \dfrac{w^{n_i}}{\kappa_i^{n_i} + w^{n_i}}$ represents Hill function of activating process. In the following we present mathematical models $M1 - M5$.

Model $M1$: transcriptional control based repressilator

$$\begin{aligned}\frac{dx}{dt} &= \beta_1 h_2(y) - r_1 x \\ \frac{dy}{dt} &= \beta_2 h_3(z) - r_2 y \\ \frac{dz}{dt} &= \beta_3 h_1(x) - r_3 z\end{aligned} \tag{2.1}$$

where x, y, z represents the concentration of genes and r_i, β_i, $i = 1, 2, 3$ are degradation rate and gene expression rate respectively.

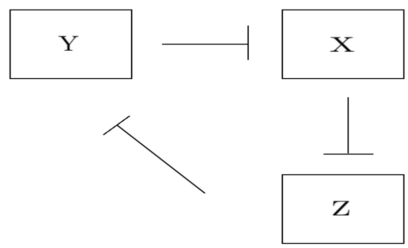

Figure 2.1

Model $M2$: Post-translational control based repressilator

$$\begin{aligned}\frac{dx}{dt} &= \beta_1 - (r_1 + r_{d1} g_2(y))x \\ \frac{dy}{dt} &= \beta_2 - (r_2 + r_{d2} g_3(z))y \\ \frac{dz}{dt} &= \beta_3 - (r_3 + r_{d3} g_1(x))z\end{aligned} \tag{2.2}$$

where r_{d_i}, $i = 1, 2, 3$, is the controlled degradation rate.

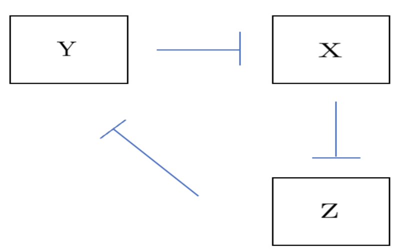

Figure 2.2

Model $M3$: Transcriptional control based repressilator with additional positive feed back

$$
\begin{aligned}
\frac{dx}{dt} &= \beta_1 h_2(y) + \beta_p g_1(x) - r_1 x \\
\frac{dy}{dt} &= \beta_2 h_3(z) - r_2 y \\
\frac{dz}{dt} &= \beta_3 h_1(x) - r_3 z
\end{aligned}
\tag{2.3}
$$

where β_p is the positive feedback rate.

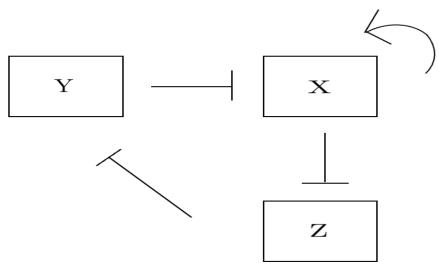

Figure 2.3

Model $M4$: Post-translational control based repressilator with additional positive feedback loop

$$
\begin{aligned}
\frac{dx}{dt} &= \beta_1 + \beta_p g_1(x) - (r_1 + r_{d1} g_2(y))x \\
\frac{dy}{dt} &= \beta_2 - (r_2 + r_{d2} g_3(z))y \\
\frac{dz}{dt} &= \beta_3 - (r_3 + r_{d3} g_1(x))z
\end{aligned}
\tag{2.4}
$$

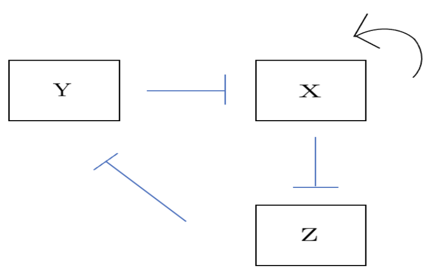

Figure 2.4

Model $M5$: Coupled transcriptional and post-translational control-based oscillator

$$\begin{aligned}\frac{dx}{dt} &= \beta_1 h_2(y) - (r_1 + r_{d1} g_2(y))x \\ \frac{dy}{dt} &= \beta_2 h_3(z) - (r_2 + r_{d2} g_3(z))y \\ \frac{dz}{dt} &= \beta_3 h_1(x) - (r_3 + r_{d3} g_1(x))z\end{aligned} \tag{2.5}$$

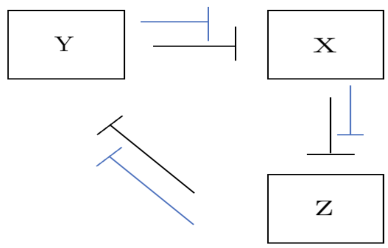

Figure 2.5

3. **Statements of Main Results.** Before we state main results we state the Poincaré-Bendixson Theorem for three-dimensional competitive systems.

Definition 3.1 : Consider the autonomous system of ordinary differential equations

$$x' = f(x), \quad x = (x_1, \cdots, x_n) \in \mathbb{R}^n \tag{E}$$

where $f = (f_i, \cdots, f_n)$ is continuously differentiable on an open set $D \subseteq \mathbb{R}^n$. The system (E) is called a competitive system on D if D is p-convex and

$$\frac{\partial f_i}{\partial x_j} \leq 0, \quad i \neq j, \quad x \in D.$$

We recall that D is p-convex if $tx + (1-t)y \in D$ for all $t \in [0,1]$ whenever $x, y \in D$ and $x \leq y$. In the following we state the Poincaré-Bendixson Theorem for three-dimensional competitive systems.

Theorem A ([27], p.41) : *A compact limit set of a competitive system in $\mathbb{R}^3$ that contains no equilibrium points is a periodic orbit.*

Next we state the main results for Model $M1$- Model $M5$.

Theorem 3.1 : *For Model $M1$, the system (2.1) satisfies:*

(i) There exists a unique positive equilibrium (x^*, y^*, z^*). Let

$$\begin{aligned}A_1 &= r_1 + r_2 + r_3, \\ A_2 &= r_1 r_2 + r_1 r_3 + r_2 r_3, \\ A_3 &= r_1 r_2 r_3 + (-\beta_1 \beta_2 \beta_3 h_1'(x^*) h_2'(y^*) h_3'(z^*)).\end{aligned} \tag{3.1}$$

(a) (x^*, y^*, z^*) is locally asymptotically stable if $A_1 A_2 > A_3$.

(b) (x^*, y^*, z^*) is unstable with one dimensional stable manifold $W^s(x^*, y^*, z^*)$ if $A_1 A_2 < A_3$.

(ii) Let

$$\frac{n_1\left(\frac{\beta_1}{r_1}\right)^{n_1}}{\kappa_1^{n_1}+\left(\frac{\beta_1}{r_1}\right)^{n_1}}\cdot\frac{n_2\left(\frac{\beta_2}{r_2}\right)^{n_2}}{\kappa_2^{n_2}+\left(\frac{\beta_2}{r_2}\right)^{n_2}}\cdot\frac{n_3\left(\frac{\beta_3}{r_3}\right)^{n_3}}{\kappa_3^{n_3}+\left(\frac{\beta_3}{r_3}\right)^{n_3}}\le 8. \tag{H1}$$

Under hypothesis (H1), the following conclusions (C1) and (C2) hold.

(C1) If (x^*,y^*,z^*) is locally asymptotically stable then (x^*,y^*,z^*) is globally asymptotically stable in $\mathbb{R}+^3$.

(C2) If (x^*,y^*,z^*) is unstable, for the trajectory with $(x(0),y(0),z(0))\notin W^s(x^*,y^*,z^*)$ tends to a limit cycle Γ.

Remark 3.1 :

(i) If $n_1n_2n_3\le 8$, then (H1) holds.

(ii) If $\frac{\beta_i}{r_i}\le 1$ for $i=1,2,3$, then for n_i large $\lim_{n_i\to\infty}\left(n_i\left(\frac{\beta_i}{r_i}\right)^{n_i}\right)=0$. Hence (H1) holds.

Theorem 3.2 : For Model $M2$, the system (2.2) satisfies:

(i) *There exists a unique positive equilibrium (x^*,y^*,z^*).* Let

$$\begin{aligned}
A_1 &= (r_1+r_{d1}g_2(y^*))+(r_2+r_{d2}g_3(z^*))+(r_3+r_{d3}g_1(x^*)),\\
A_2 &= (r_1+r_{d1}g_2(y^*))(r_2+r_{d2}g_3(z^*))+(r_1+r_{d1}g_2(y^*))(r_3+r_{d3}g_1(x^*))\\
&\quad +(r_2+r_{d2}g_3(z^*))(r_3+r_{d3}g_1(x^*)),\\
A_3 &= (r_1+r_{d1}g_2(y^*))(r_2+r_{d2}g_3(z^*))(r_3+r_{d3}g_1(x^*))\\
&\quad +r_{d1}g_2'(y^*)x^*r_{d2}g_3'(z^*)y^*r_{d3}g_1'(x^*)z^*.
\end{aligned} \tag{3.2}$$

Then (a) and (b) of Theorem 3.1(i) holds.

(ii) If $n_1=n_2=n_3=1$ and

$$r_{d1}r_{d2}r_{d3}\frac{\kappa_1\kappa_2\kappa_3}{\beta_1\beta_2\beta_3}\le 8 \tag{H2}$$

or $n_i>1$, $i=1,2,3$ and

$$\frac{r_{d1}r_{d2}r_{d3}}{\beta_1\beta_2\beta_3}\prod_{i=1}^{3}\frac{\kappa_i(n_i+1)(n_i-1)\sqrt[n_i]{\frac{n_i+1}{n_i-1}}}{4n_i}\le 8. \tag{H3}$$

Then under hypothesis (H2) or (H3), the conclusions (C1) and (C2) of Theorem 3.1(ii) hold.

Remark 3.2 : If $n_1=n_2=n_3=2$, then (H3) implies

$$\frac{r_{d1}r_{d2}r_{d3}}{\beta_1\beta_2\beta_3}\frac{3\sqrt{3}}{8}\kappa_1\frac{3\sqrt{3}}{8}\kappa_2\frac{3\sqrt{3}}{8}\kappa_3\le 8.$$

Theorem 3.3 : *Assume*

$$r_1x>\beta_pg_1(x),\ \textit{and } r_1>\beta_pg_1'(x),\ \textit{for all } x>0. \tag{$\widehat{M}3$}$$

For Model $M3$, the system (2.3) satisfies:

(i) There exists a unique positive equilibrium (x^*, y^*, z^*). Let

$$\begin{aligned} A_1 &= r_1 - \beta_p g_1'(x^*) + r_2 + r_3 > 0 \\ A_2 &= (r_1 - \beta_p g_1'(x^*))r_2 + (r_1 - \beta_p g_1'(x^*))r_3 + r_2 r_3 > 0 \\ A_3 &= (r_1 - \beta_p g_1'(x^*))r_2 r_3 + (-\beta_1\beta_2\beta_3 h_1'(x^*)h_2'(y^*)h_3'(z^*)) > 0. \end{aligned} \tag{3.3}$$

Then (a) and (b) of Theorem 3.1(i) hold.

(ii) Let (H1) hold. Then the conclusions (C1) and (C2) of Theorem 3.1(ii) hold.

Remark 3.3 : ($\widehat{\mathrm{M}}3$) says the positive feedback term $\beta_p g_1(x)$ in the system (2.3) is small. From [32] Model $M3$ is more robust than Model $M1$ in the sense of producing oscillations.

Theorem 3.4 : *Assume*

$$\begin{aligned} & xg_1'(x) - g_1(x) < \frac{\beta_1}{\beta_p},\ x > 0 \text{ for } \beta_p > 0 \text{ sufficiently small,} \\ & \beta_p < \frac{1}{\beta_1} \max_{\widetilde{x}_1 < x < \widetilde{x}_2} (xg_1'(x) - g_1(x)) \text{ where} \\ & xg_1'(x) - g_1(x) < 0 \text{ for } 0 < x < \widetilde{x}_1 \text{ or } x > \widetilde{x}_2, \\ & xg_1'(x) - g_1(x) > 0 \text{ for } \widetilde{x}_1 < x < \widetilde{x}_2. \end{aligned} \tag{$\widehat{M}4$}$$

For Model $M4$, the system (2.4) satisfies:

(i) There exists a unique positive equilibrium (x^*, y^*, z^*). Let

$$\begin{aligned} \widetilde{r}_1 &= r_1 + r_{d1}g_2(y^*) - \beta_p g_1'(x^*) \\ \widetilde{r}_2 &= r_2 + r_{d2}g_3(z^*) \\ \widetilde{r}_3 &= r_3 + r_{d3}g_1(x^*), \end{aligned}$$

and

$$\begin{aligned} A_1 &= \widetilde{r}_1 + \widetilde{r}_2 + \widetilde{r}_3 > 0 \\ A_2 &= \widetilde{r}_1\widetilde{r}_2 + \widetilde{r}_3\widetilde{r}_3 + \widetilde{r}_1\widetilde{r}_3 > 0 \\ A_3 &= \widetilde{r}_1\widetilde{r}_2\widetilde{r}_3 + r_{d1}r_{d2}r_{d3}g_1'(x^*)g_2'(y^*)g_3'(z^*)x^*y^*z^* > 0. \end{aligned} \tag{3.4}$$

Then (a) and (b) of Theorem 3.1(i) holds.

(ii) If

$$\prod_{i=1}^{3} r_{di} \frac{\kappa_i(n_i+1)(n_i-1)\sqrt[n_i]{\dfrac{n_i+1}{n_i-1}}}{4n_i} \le 8\beta_1\beta_2(\beta_1 + \beta_p g_1(x_{low})) \tag{H4}$$

where x_{low} is the root of

$$\beta_1 + \beta_p g_1(X) = \left(r_1 + r_{d1}g_2\left(\frac{\beta_2}{r_2}\right)\right)X,$$

and x_{low} is a lower bound of $X(t)$. Then the conclusions (C1) and (C2) of Theorem 3.1(ii) hold.

Remark 3.4 : ($\widehat{\mathrm{M}}4$) says the positive feedback term in the system (2.4) is small. From [32] the Model $M4$ is more robust that the Model $M2$ in producing oscillations.

Theorem 3.5 : *For Model $M5$, the system (2.5) satisfies:*

(i) There exists a unique positive equilibrium (x^*, y^*, z^*). Let

$$\begin{aligned}\widetilde{r}_1 &= r_1 + r_{d1} g_2(y^*)\\ \widetilde{r}_2 &= r_2 + r_{d2} g_3(z^*)\\ \widetilde{r}_3 &= r_3 + r_{d3} g_1(x^*),\end{aligned}$$

and

$$\begin{aligned}A_1 &= \widetilde{r}_1 + \widetilde{r}_3 + \widetilde{r}_3,\\ A_2 &= \widetilde{r}_1\widetilde{r}_2 + \widetilde{r}_2\widetilde{r}_3 + \widetilde{r}_1\widetilde{r}_3,\\ A_3 &= \widetilde{r}_1\widetilde{r}_2\widetilde{r}_3\\ &\quad + (r_{d1} g_2'(y^*) x^* - \beta_1 h_2'(y^*))(r_{d2} g_3'(z^*) y^* - \beta_2 h_3'(z^*))(r_{d3} g_1'(x^*) z^* - \beta_3 h_1'(x^*)).\end{aligned} \tag{3.5}$$

Then (a) and (b) of Theorem 3.1(i) hold.

(ii) Let

$$\begin{aligned}8\beta_1\beta_2\beta_3 \geq &\left(n_2 g_2\left(\frac{\beta_2}{r_2}\right)\right)\left(\beta_1 + r_{d1}\frac{\beta_1}{r_1}\right)\\ &\cdot\left(n_1 g_1\left(\frac{\beta_1}{r_1}\right)\right)\left(\beta_3 + r_{d3}\frac{\beta_3}{r_3}\right)\\ &\cdot\left(n_3 g_3\left(\frac{\beta_3}{r_3}\right)\right)\left(\beta_2 + r_{d2}\frac{\beta_2}{r_2}\right).\end{aligned} \tag{H5}$$

If (H5) holds, then the conclusions (C1) and (C2) of Theorem 3.1(ii) hold.

Remark 3.5 : If

$$\left(1 + \frac{r_{d1}}{r_1}\right)\left(1 + \frac{r_{d3}}{r_3}\right)\left(1 + \frac{r_{d2}}{r_2}\right) n_1 n_2 n_3 \leq 8, \tag{H6}$$

then (H5) holds.

4. **Numerical Test Results and Discussion.** With the mathematical analysis presented above, we numerically test whether oscillation can be produced following the derived criteria. Following [15], we have extended the same parameter range as listed in Table 1 for both $M1$ (and $M5$), finding parameter sets that satisfy criteria (H1) (and (H5)) and test for oscillations. Among 100,000 parameter sets each for $M1$ and $M5$ satisfying (H1) and (H5), we could not identify any parameter set that can oscillate continuously. Unfortunately, the theorem presented in the present work is not sufficient to identify oscillators.

It will be a challenge to prove uniqueness of limit cycles in the 3-dimensional competitive systems. So far there is no such results in the literature. However in [33], [11] the authors prove multiple limit cycles in some three species Lotka-Volterra competitive models. We shall investigate uniqueness of limit cycles for the model $M1$-$M5$ in our future project.

(1) For Model $M1$:

The parameters $\beta_1 = 10$, $\beta_2 = 20$, $\beta_3 = 35$, $n_1 = 2$, $n_2 = 2$, $n_3 = 2$, $\kappa_1 = 1$, $\kappa_2 = 2$, $\kappa_3 = 2.5$, $r_1 = 1$, $r_2 = 2$, $r_3 = 2.5$ satisfy (H1) and the trajectory with initial condition $x(0) = 1$, $y(0) = 1$, $z(0) = 1$ goes to equilibrium (x^*, y^*, z^*) as $t \to \infty$. Hence (x^*, y^*, z^*) is globally asymptotically stable (See Fig. 4.1 (a)).

TABLE 1. The scanned parameter range

$M1$		
Parameters	Range	Search scale
r_i (degradation rates)	0.001-1000	Logarithm
β_i (gene expression rates)	0.001-1000	Logarithm
κ (Threshold in all Hill function)	0.001-1000	Logarithm
n (in the Hill function)	1-8	Linear
$M5$		
r_i (basal degradation rates)	0.001-1000	Logarithm
r_{di} (controlled degradation rates)	0.001-1000	Logarithm
β_i (gene expression rates)	0.001-1000	Logarithm
κ (Threshold in all Hill function)	0.001-1000	Logarithm
n (in the Hill function)	1-8	Linear

In Fig. 4.1 (b), the trajectory approaches a limit cycle, however the parameters $\beta_1 = 10$, $\beta_2 = 20$, $\beta_3 = 35$, $n_1 = 3$, $n_2 = 3$, $n_3 = 3$, $\kappa_1 = 1$, $\kappa_2 = 2$, $\kappa_3 = 2.5$, $r_1 = 1$, $r_2 = 2$, $r_3 = 2.5$ does not satisfy (H1)

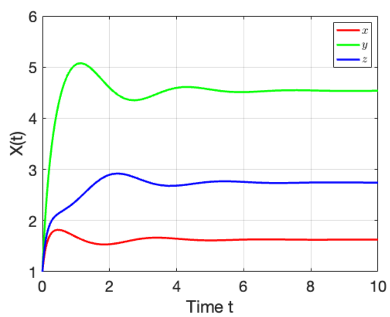

Fig 4.1 (a)

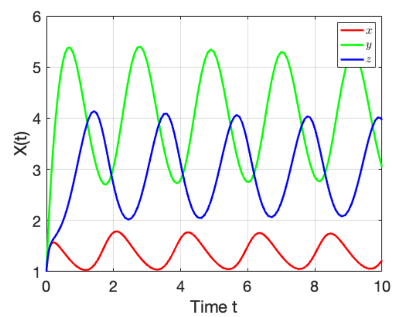

Fig 4.1 (b)

1. For Model $M2$:

   [] The parameters $\beta_1 = 10$, $\beta_2 = 20$, $\beta_3 = 25$, $n_1 = 2$, $n_2 = 2$, $n_3 = 2$, $\kappa_1 = 2$, $\kappa_2 = 2$, $\kappa_3 = 2.5$, $r_1 = 1$, $r_2 = 2$, $r_3 = 3$, $r_{d1} = 5$, $r_{d2} = 10$, $r_{d3} = 15$ satisfy (H3) and the trajectory with initial condition $x(0) = 1$, $y(0) = 1$, $z(0) = 1$ goes to equilibrium (x^*, y^*, z^*) as $t \to \infty$. Hence (x^*, y^*, z^*) is globally asymptotically stable (See Fig. 4.2 (a)).

   In Fig. 4.2 (b), the trajectory approaches a limit cycle, however the parameters $\beta_1 = 10$, $\beta_2 = 20$, $\beta_3 = 25$, $n_1 = 5$, $n_2 = 5$, $n_3 = 5$, $\kappa_1 = 2$, $\kappa_2 = 2$, $\kappa_3 = 2.5$, $r_1 = 1$, $r_2 = 2$, $r_3 = 3$, $r_{d1} = 50$, $r_{d2} = 100$, $r_{d3} = 150$ does not satisfy (H3)
2. For Model $M3$:

   The parameters $\beta_1 = 10$, $\beta_2 = 20$, $\beta_3 = 25$, $n_1 = 2$, $n_2 = 2$, $n_3 = 2$, $\kappa_1 = 1$, $\kappa_2 = 2$, $\kappa_3 = 2.5$, $r_1 = 5$, $r_2 = 10$, $r_3 = 12.5$, $\beta_p = 5$ satisfy (H1) and the trajectory with initial condition $x(0) = 1$, $y(0) = 1$, $z(0) = 1$ goes to equilibrium (x^*, y^*, z^*) as $t \to \infty$. Hence (x^*, y^*, z^*) is globally asymptotically stable (See Fig. 4.3 (a)).

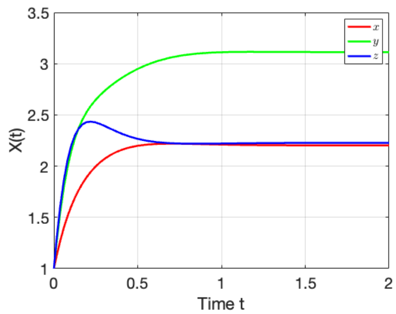

Fig 4.2 (a)

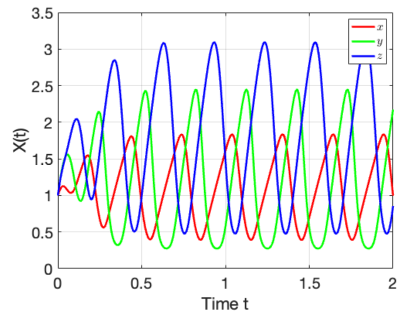

Fig 4.2 (b)

In Fig. 4.3 (b), the trajectory approaches a limit cycle, however the parameters $\beta_1 = 50$, $\beta_2 = 100$, $\beta_3 = 120$, $n_1 = 5$, $n_2 = 5$, $n_3 = 5$, $\kappa_1 = 1$, $\kappa_2 = 2$, $\kappa_3 = 2.5$, $r_1 = 5$, $r_2 = 10$, $r_3 = 12.5$, $\beta_p = 5$ does not satisfy (H1)

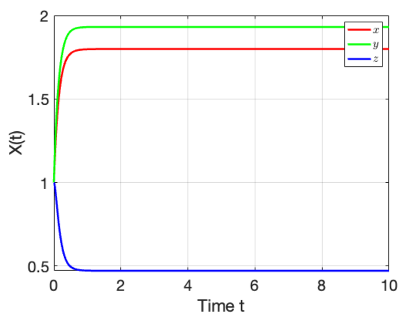

Fig 4.3 (a)

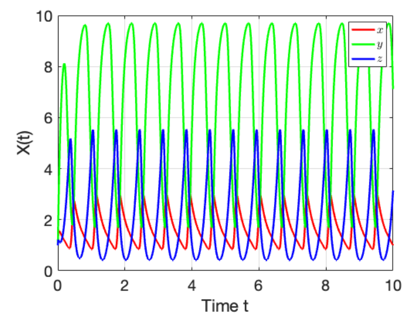

Fig 4.3 (b)

3. For Model $M4$:

   The parameters $\beta_1 = 10$, $\beta_2 = 20$, $\beta_3 = 25$, $n_1 = 2$, $n_2 = 2$, $n_3 = 2$, $\kappa_1 = 2$, $\kappa_2 = 2$, $\kappa_3 = 2.5$, $r_1 = 1$, $r_2 = 2$, $r_3 = 3$, $r_{d1} = 5$, $r_{d2} = 10$, $r_{d3} = 15$, $\beta_p = 0.5$ satisfy (H4) and the trajectory with initial condition $x(0) = 1$, $y(0) = 1$, $z(0) = 1$ goes to equilibrium (x^*, y^*, z^*) as $t \to \infty$. Hence (x^*, y^*, z^*) is globally asymptotically stable (See Fig. 4.4 (a)).

   In Fig. 4.4 (b), the trajectory approaches a limit cycle, however the parameters $\beta_1 = 10$, $\beta_2 = 20$, $\beta_3 = 25$, $n_1 = 5$, $n_2 = 5$, $n_3 = 5$, $\kappa_1 = 1$, $\kappa_2 = 2$, $\kappa_3 = 2.5$, $r_1 = 1$, $r_2 = 2$, $r_3 = 3$, $r_{d1} = 50$, $r_{d2} = 100$, $r_{d3} = 150$, $\beta_p = 0.5$ does not satisfy (H4)
4. For Model $M5$:

   The parameters $\beta_1 = 10$, $\beta_2 = 20$, $\beta_3 = 25$, $n_1 = 2$, $n_2 = 2$, $n_3 = 2$, $\kappa_1 = 2$, $\kappa_2 = 2$, $\kappa_3 = 2.5$, $r_1 = 1$, $r_2 = 2$, $r_3 = 3$, $r_{d1} = 0.01$, $r_{d2} = 0.02$, $r_{d3} = 0.03$ satisfy (H5) and the trajectory with initial condition $x(0) = 1$, $y(0) = 1$, $z(0) = 1$ goes to equilibrium (x^*, y^*, z^*) as $t \to \infty$. Hence (x^*, y^*, z^*) is globally asymptotically stable (See Fig. 4.5 (a)).

   In Fig. 4.5 (b), the trajectory approaches a limit cycle, however the parameters $\beta_1 = 10$, $\beta_2 = 20$, $\beta_3 = 25$, $n_1 = 5$, $n_2 = 5$, $n_3 = 5$, $\kappa_1 = 1$, $\kappa_2 = 2$, $\kappa_3 = 2.5$, $r_1 = 1$, $r_2 = 2$, $r_3 = 3$, $r_{d1} = 50$, $r_{d2} = 100$, $r_{d3} = 150$ does not satisfy (H5)

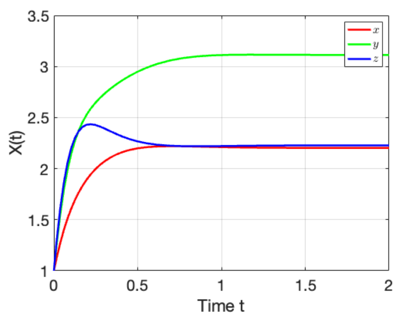

Fig 4.4 (a)

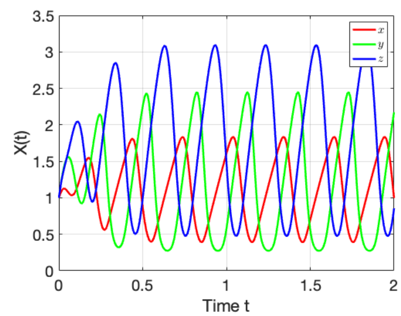

Fig 4.4 (b)

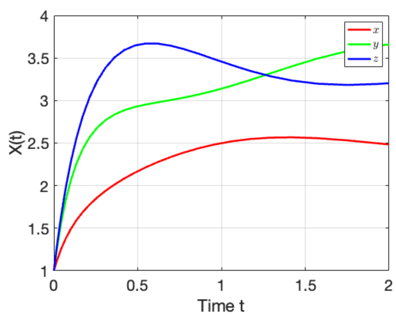

Fig 4.5 (a)

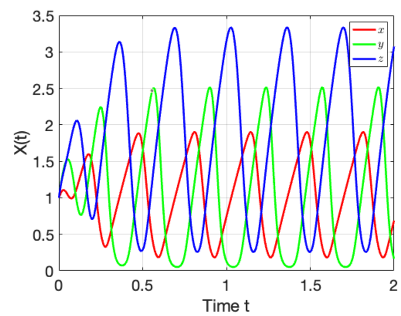

Fig 4.5 (b)

5. **Proofs.** For the three-dimensional competitive systems in Models $M1-M5$, the Poincaré-Bendixson Theorem holds (See Theorem A in Section 3). We shall apply the second-compound method [20] to show that under some conditions stated in Theorem 3.1 - Theorem 3.5 every periodic orbit, if it exists, is orbitally asymptotically stable. Since the positive equilibrium (x^*, y^*, z^*) is unique for each model of $M1 - M5$, then it follows that

(i) By Theorem 5.2 (See below), the equilibrium (x^*, y^*, z^*) is globally asymptotically stable when (x^*, y^*, z^*) is locally asymptotically stable.

(ii) When (x^*, y^*, z^*) is unstable, then (x^*, y^*, z^*) has one-dimensional stable manifold $W^s(x^*, y^*, z^*)$. For the trajectory with

$$(x(0), y(0), z(0)) \notin W^s(x^*, y^*, z^*),$$

the orbit tends to a limit cycle Γ.

Let's recall that for a 3×3 matrix is

$$A = \begin{bmatrix} a_{11} & a_{12} & a_{13} \\ a_{21} & a_{22} & a_{23} \\ a_{31} & a_{32} & a_{33} \end{bmatrix}$$

the second compound matrix of A is

$$A^{[2]} = \begin{bmatrix} a_{11} + a_{22} & a_{23} & -a_{13} \\ a_{32} & a_{11} + a_{33} & a_{12} \\ -a_{31} & a_{21} & a_{22} + a_{33} \end{bmatrix}.$$

Let $(X(t), Y(t), Z(t))$ be a ω-periodic solution of three dimensional competitive system

$$x' = F(x), \quad x \in \mathbb{R}^3. \tag{5.1}$$

Let

$$A = DF(X, Y, Z), \text{ Jacobian matrix at } (X, Y, Z),$$

and

$$A^{[2]} = DF^{[2]}(X, Y, Z).$$

Consider the ω-periodic linear equation

$$\frac{dU}{dt} = DF^{[2]}(X, Y, Z)U. \tag{5.2}$$

From [27, Theorem 4.2] (See also [17], Theorem 3.1):

Theorem 5.1([20]) **:** *A sufficient condition for a periodic orbit $\gamma = \{p(t) : 0 \le t \le \omega\}$ of (5.1) to be asymptotically orbitally stable with asymptotic phase is that the linear periodic system (5.2) is asymptotically stable.*

We shall introduce a function

$$W(X, Y, Z; U) = \sum_{i=1}^{3} p_i(X, Y, Z)|U_i|$$

where $p_i(X, Y, Z)$ for $i = 1, 2, 3$ are auxiliary positive smooth functions, which will be determined latter. Let

$$W(t) = W(X(t), Y(t), Z(t); U(t)).$$

We shall prove $W(t) \to 0$ as $t \to \infty$, i.e. the periodic linear system (5.2) is asymptotically stable. Then the periodic orbit

$$\{(X(t), Y(t), Z(t)) : 0 \le t \le \omega\}$$

is asymptotically orbitally stable.

For the sake of completeness, we include the proof of global asymptotically stability of the unique positive equilibrium E_c in [13], Prop. 3.6. Let $\Omega \subseteq \mathrm{Int}(\mathbb{R}^3_+)$ be a bounded positively invariant region for the three-dimensional competitive system (5.1).

Theorem 5.2([13]) **:** *Assume every periodic orbit of the system (5.1), if it exists, is orbitally asymptotically stable. Let E_c be a locally asymptotically stable equilibrium of (5.1) in Ω. Then E_c is globally asymptotically stable in Ω.*

Proof. Let $\mathcal{A}$ be the basin of attraction of the locally asymptotically stable equilibrium E_c. Then $\mathcal{A}$ is a nonempty relatively open subset of Ω. Denote $\partial_\Omega \mathcal{A}$ the boundary of $\mathcal{A}$ relative to Ω. Clearly $\partial_\Omega \mathcal{A}$ is invariant. Let $u \in \partial_\Omega \mathcal{A}$. Them the omega-limit set $\omega(u) \subseteq \partial_\Omega \mathcal{A}$ and $E_c \notin \omega(u)$. Since E_c is the unique positive equilibrium in Ω. By Poincaré-Bendixson Theorem $\omega(u)$ is a periodic orbit of (5.1), $\omega(u) \subseteq \partial_\Omega \mathcal{A}$. From the assumption $\omega(u)$ is orbitally asymptotically stable. One can choose a point $p \in \mathcal{A}$ sufficiently close to $\omega(u)$. On one hand, p is attracted to E_c. On the other hand, p will be asymptotic to the orbitally stable periodic orbit $\omega(u)$, a contradiction. Thus we prove that E_c is globally asymptotically stable in Ω. ∎

Proof of Theorem 3.1 :

(i) The positive equilibrium (x^*, y^*, z^*) satisfies

$$x = \frac{1}{r_1}\beta_1 h_2(y),\ y = \frac{1}{r_2}\beta_2 h_3(z),\ z = \frac{1}{r_3}\beta_3 h_1(x).$$

Then

$$\begin{aligned} z &= \frac{1}{r_3}\beta_3 h_1\left(\frac{1}{r_1}\beta_1 h_2\left(\frac{1}{r_2}\beta_2 h_3(z)\right)\right) := H(z), \\ H(0) &= \frac{\beta_3}{r_3}\left(\frac{\beta_1}{r_1}h_2\left(\frac{\beta_2}{r_2}h_3(0)\right)\right) \\ &= \frac{\beta_3}{r_3}\left(\frac{\beta_1}{r_1}h_2\left(\frac{\beta_2}{r_2}\right)\right) > 0. \end{aligned}$$

Obviously

$$H'(z) = \frac{1}{r_3}\beta_3 h_1'\left(\frac{\beta_1}{r_1}h_2\left(\frac{\beta_2}{r_2}h_3(z)\right)\right)\cdot\frac{\beta_1}{r_1}h_1'\left(\frac{\beta_2}{r_2}h_3(z)\right)\cdot\frac{\beta_2}{r_2}h_3'(z) < 0.$$

Thus $z = H(z)$ has a unique positive solution z^*. Then $y^* = \frac{\beta_2}{r_2}h_3(z^*)$, $x^* = \frac{\beta_1}{r_1}h_2(y^*)$. Hence the positive equilibrium (x^*, y^*, z^*) is unique.

The Jacobian evaluated at (x^*, y^*, z^*) is

$$J(x^*, y^*, z^*) = \begin{bmatrix} -r_1 & \beta_1 h_2'(y^*) & 0 \\ 0 & -r_2 & \beta_2 h_3'(z^*) \\ \beta_3 h_1'(x^*) & 0 & -r_3 \end{bmatrix}$$

with eigenvalues λ_1, λ_2, and λ_3. The characteristic polynomial of $J(x^*, y^*, z^*)$ is

$$\begin{aligned} f(\lambda) =& \lambda^3 + \lambda^2(r_1 + r_2 + r_3) + \lambda(r_1r_2 + r_1r_3 + r_2r_3) + \\ & (r_1r_2r_3 + (-\beta_1\beta_2\beta_3 h_1'(x^*)h_2'(y^*)h_3'(z^*))). \end{aligned}$$

From Routh-Hurwitz criteria [12], page 58, (x^*, y^*, z^*) is locally asymptotically stable if $A_1A_2 > A_3$ where

$$\begin{aligned} &A_1 = r_1 + r_2 + r_3,\ A_2 = r_1r_2 + r_1r_3 + r_2r_3, \\ &A_3 = r_1r_2r_3 + (-\beta_1\beta_2\beta_3 h_1'(x^*)h_2'(y^*)h_3'(z^*)). \end{aligned}$$

If $A_1A_2 < A_3$, then $\det J = -f(0) = \lambda_1\lambda_2\lambda_3 < 0$. From [27] (p.51, Prop. 6.1) below, then (a) and (b) hold.

Prop. 6.1 : Suppose $p = (x^*, y^*, z^*)$ is hyperbolic and unstable. Then the stable manifold of p, $W^s(p)$ is one dimensional and the ω-limit set $\omega(q)$ is a nontrivial periodic orbit in D for every $q \in D \setminus W^s(p)$.

(ii) Let $(X(t), Y(t), Z(t))$ be a ω-periodic solution of (2.1). We denote F the vector field of (2.1). Then the Jacobian matrix $DF(X, Y, Z)$ is

$$\begin{pmatrix} -r_1 & \beta_1 h_2'(Y) & 0 \\ 0 & -r_2 & \beta_2 h_3'(Z) \\ \beta_3 h_1'(X) & 0 & -r_3 \end{pmatrix}. \tag{5.3}$$

Then the second compound matrix $DF^{[2]}(X, Y, Z)$ is

$$DF^{[2]}(X, Y, Z) = \begin{bmatrix} -r_1 - r_2 & \beta_2 h_3'(Z) & 0 \\ 0 & -r_1 - r_3 & \beta_1 h_2'(Y) \\ -\beta_3 h_1'(X) & 0 & -r_2 - r_3 \end{bmatrix}. \tag{5.4}$$

Consider ω-periodic linear equation

$$\frac{dU}{dt} = DF^{[2]}(X,Y,Z)U,\, U = (U_1, U_2, U_3). \tag{5.5}$$

Now, we introduce the function

$$W(X,Y,Z;U) = \sum_{i=1}^{3} p_i(X,Y,Z)|U_i|$$

where $p_i(X,Y,Z)$, $i = 1,2,3$ will be auxiliary positive smooth functions, which will be determined later. Let $W(t) = W(X(t),Y(t),Z(t);U(t))$. Then the right hand side derivative $D_+W(t)$ of $W(t)$ with respect to t exists and has the form

$$D_+W(t) = \sum_{i=1}^{3} p_i'(t)|U_i(t)| + p_i(t)D_+(|U_i(t)|) \tag{5.6}$$

where $p_i(t) = p_i(X(t),Y(t),Z(t))$ and $p_i'(t)$ is the derivative of $p_i(t)$. From (5.5), we have

$$\begin{aligned}
\frac{dU_1}{dt} &= (-r_1 - r_2)U_1(t) + \beta_2 h_3'(Z(t))U_2(t)\\
\frac{dU_2}{dt} &= (-r_1 - r_3)U_2(t) + \beta_1 h_2'(Y(t))U_3(t)\\
\frac{dU_3}{dt} &= (-\beta_3 h_1'(X(t)))U_1(t) + (-r_2 - r_3)U_3(t).
\end{aligned}$$

Since the diagonals of the matrix $DF^{[2]}(X,Y,Z)$ are negative, it follows that

$$\begin{aligned}
D_+(|U_1(t)|) &\le -(r_1 + r_2)|U_1(t)| + (-\beta_2 h_3'(Z(t)))|U_2(t)|\\
D_+(|U_2(t)|) &\le -(r_1 + r_3)|U_2(t)| + (-\beta_1 h_2'(Y(t)))|U_3(t)|\\
D_+(|U_3(t)|) &\le -(r_2 + r_3)|U_3(t)| + (-\beta_3 h_1'(X(t)))|U_1(t)|
\end{aligned} \tag{5.7}$$

From (5.6) and (5.7), a direct calculation yields

$$\begin{aligned}
D_+W(t) \le{}& \left(\frac{p_1'(t)}{p_1(t)} - (r_1 + r_2) + \frac{p_3(t)}{p_1(t)}(-\beta_3 h_1'(X(t)))\right) p_1(t)|U_1(t)|\\
&+ \left(\frac{p_2'(t)}{p_2(t)} + \frac{p_1(t)}{p_2(t)}(-\beta_2 h_3'(Z(t))) - (r_1 + r_3)\right) p_2(t)|U_2(t)|\\
&+ \left(\frac{p_3'(t)}{p_3(t)} + \frac{p_2(t)}{p_3(t)}(-\beta_1 h_2'(Y(t))) - (r_2 + r_3)\right) p_3(t)|U_3(t)|.
\end{aligned} \tag{5.8}$$

From (5.1), the periodic solution $(X(t),Y(t),Z(t))$ satisfies

$$\begin{aligned}
\frac{dX}{dt} &= \beta_1 h_2(Y) - r_1 X\\
\frac{dY}{dt} &= \beta_2 h_3(Z) - r_2 Y\\
\frac{dZ}{dt} &= \beta_3 h_1(X) - r_3 Z.
\end{aligned} \tag{5.9}$$

From (5.9), it follows that

$$\begin{aligned}\int_0^\omega \left(\frac{\beta_1 h_2(Y(t))}{X(t)} - r_1\right) dt = 0\\ \int_0^\omega \left(\frac{\beta_2 h_3(Z(t))}{Y(t)} - r_2\right) dt = 0\\ \int_0^\omega \left(\frac{\beta_3 h_1(X(t))}{Z(t)} - r_3\right) dt = 0.\end{aligned} \tag{5.10}$$

Now, by choosing $p_3 = \frac{1}{p_1} := p > 0$ where $p = p(X, Y, Z)$ is a positive function of the stable variable (X, Y, Z). We note that along the ω-periodic solution $(X(t), Y(t), Z(t))$, $t \in [0, \omega]$, one has

$$\int_0^\omega \frac{p'}{p} dt = \int_0^\omega \frac{p_2'}{p_2} dt = 0.$$

Let

$$\begin{aligned} g_1(t) &= \frac{p'(t)}{p(t)} - \left(\frac{\beta_1 h_2(Y)}{X} + \frac{\beta_2 h_3(Z)}{Y}\right) + \frac{p_3}{p_1}(-\beta_3 h_1'(X))\\ g_2(t) &= \frac{p_2'(t)}{p_2(t)} + \frac{p}{p_2}(-\beta_3 h_3'(Z)) - \left(\frac{\beta_1 h_2(Y)}{X} + \frac{\beta_3 h_1(X)}{Z}\right)\\ g_3(t) &= \frac{p_3'(t)}{p_3(t)} + \frac{p_2}{p_3}(-\beta_1 h_2'(Y)) - \left(\frac{\beta_2 h_3(Z)}{Y} + \frac{\beta_3 h_1(X)}{Z}\right). \end{aligned}$$

Choose

$$p = \sqrt{\frac{\dfrac{\beta_1 h_2(Y)}{X} + \dfrac{\beta_2 h_3(Z)}{Y}}{-\beta_3 h_3'(X)}}.$$

Then $\int_0^\omega g_1(t)dt = 0$. Consequently, from (5.8)

$$D_+ W \le \max\left(g_1(t), g_2(t), g_3(t)\right) W(t). \tag{5.11}$$

Choose $p_2(t)$ such that

$$\begin{aligned}\frac{1/p}{p_2} &\le \frac{\dfrac{\beta_1 h_2(Y)}{X} + \dfrac{\beta_2 h_3(Z)}{Y}}{-\beta_3 h_3'(Z)}\\ \frac{p_2}{p} &\le \frac{\dfrac{\beta_2 h_3(Z)}{Y} + \dfrac{\beta_3 h_1(X)}{Z}}{-\beta_1 h_2'(Y)}.\end{aligned}$$

We need

$$\frac{(-\beta_3 h_3'(Z))(-\beta_1 h_2'(Y))}{\left(\dfrac{\beta_1 h_2(Y)}{X} + \dfrac{\beta_2 h_3(Z)}{Y}\right)\left(\dfrac{\beta_2 h_3(Z)}{Y} + \dfrac{\beta_3 h_1(X)}{Z}\right)} \le p^2 = \frac{\dfrac{\beta_1 h_2(Y)}{X} + \dfrac{\beta_2 h_3(Z)}{Y}}{-\beta_3 h_1'(X)}. \tag{5.12}$$

Then we choose p_2 such that

$$A := \frac{1}{p} \cdot \frac{-\beta_3 h_3'(Z)}{\dfrac{\beta_1 h_2(Y)}{X} + \dfrac{\beta_2 h_3(Z)}{Y}} \le p_2 \le \frac{\dfrac{\beta_2 h_3(Z)}{Y} + \dfrac{\beta_3 h_1(X)}{Z}}{-\beta_1 h_2'(Y)} \cdot p := B.$$

Say $p_2 = \frac{1}{2}(A+B)$. To show that (5.12) holds, it suffices to show

$$(-\beta_1 h_2'(Y))(-\beta_2 h_3'(Z))(-\beta_3 h_1'(X)) \leq \left(\frac{\beta_1 h_2(Y)}{X} + \frac{\beta_2 h_3(Z)}{Y}\right)\left(\frac{\beta_1 h_2(Y)}{X} + \frac{\beta_3 h_1(X)}{Z}\right)\left(\frac{\beta_2 h_3(Z)}{Y} + \frac{\beta_3 h_1(X)}{Z}\right).$$

Use the inequality, for positive numbers a and b

$$\sqrt{ab} \leq \frac{a+b}{2}.$$

It suffices to show

$$\begin{aligned}
&(-\beta_1 h_2'(Y))(-\beta_2 h_3'(Z))(-\beta_3 h_1'(X)) \\
\leq& 8\sqrt{\frac{\beta_1 h_2(Y)\beta_2 h_3(Z)}{XY}}\sqrt{\frac{\beta_1 h_2(Y)\beta_3 h_1(X)}{XZ}}\sqrt{\frac{\beta_2 h_3(Z)\beta_3 h_1(X)}{YZ}} \\
=& 8\,\frac{\beta_1\beta_2\beta_3 h_1(X)h_2(Y)h_3(Z)}{XYZ}
\end{aligned}$$

$\iff$

$$\beta_1 \frac{\kappa_2^{n_2} n_2 Y^{n_2-1}}{(\kappa_2^{n_2}+Y^{n_2})^2}\beta_3 \frac{\kappa_1^{n_1} n_1 X^{n_1-1}}{(\kappa_1^{1_2}+X^{n_1})^2}\beta_2 \frac{\kappa_3^{n_3} n_3 Z^{n_3-1}}{(\kappa_3^{n_3}+Z^{n_3})^2} \leq 8\,\frac{\beta_1\beta_2\beta_3 \dfrac{\kappa_1^{n_1}}{\kappa_1^{n_1}+X^{n_1}}\dfrac{\kappa_2^{n_2}}{\kappa_2^{n_2}+Y^{n_2}}\dfrac{\kappa_3^{n_3}}{\kappa_3^{n_3}+Z^{n_3}}}{XYZ}$$

$\iff$

$$\frac{n_1 X^{n_1}}{\kappa_1^{n_1}+X^{n_1}} \cdot \frac{n_2 Y^{n_2}}{\kappa_2^{n_2}+Y^{n_2}} \cdot \frac{n_3 Z^{n_3}}{\kappa_3^{n_3}+Z^{n_3}} \leq 8 \tag{5.13}$$

Under (5.13) we have

$$\int_0^\omega g_i(t)dt < 0,\ i=2,3,\ \int_0^\omega g_1(t)dt = 0. \tag{5.14}$$

From the first equation in (2.1), we obtain an upper bound for a periodic solution $X(t)$:

$$\frac{dX}{dt} \leq \beta_1 h_2(0) - r_1 X = \beta_1 - r_1 X,\ X(t) \leq \frac{\beta_1}{r_1}.$$

Similarly for periodic solutions $Y(t)$ and $Z(t)$, we have

$$Y(t) \leq \frac{\beta_2}{r_2} \text{ and } Z(t) \leq \frac{\beta_3}{r_3}. \tag{5.15}$$

Let

$$\frac{n_1\left(\frac{\beta_1}{r_1}\right)^{n_1}}{\kappa_1^{n_1}+\left(\frac{\beta_1}{r_1}\right)^{n_1}} \cdot \frac{n_2\left(\frac{\beta_2}{r_2}\right)^{n_2}}{\kappa_2^{n_2}+\left(\frac{\beta_2}{r_2}\right)^{n_2}} \cdot \frac{n_3\left(\frac{\beta_3}{r_3}\right)^{n_3}}{\kappa_3^{n_3}+\left(\frac{\beta_3}{r_3}\right)^{n_3}} \leq 8. \tag{H1}$$

Then (H1) implies (5.13). Under assumption (H1), from Theorem 5.1 and (5.11), (5.14), every periodic orbit $(X(t), Y(t), Z(t))$ is orbitally asymptotically stable. From the system (2.1), we obtain differential inequalities,

$$\frac{dx}{dt} \leq \beta_1 - r_1 x,\ \frac{dy}{dt} \leq \beta_2 - r_2 y,\ \frac{dz}{dt} \leq \beta_3 - r_3 z.$$

Thus if $A_1A_2 > A_3$, applying Theorem 5.2 with

$$\Omega = \left\{(x, y, z) \,:\, 0 < x < \frac{\beta_1}{r_1},\, 0 < y < \frac{\beta_2}{r2},\, 0 < z < \frac{\beta_3}{r_3}\right\} \tag{5.16}$$

yields that (x^*, y^*, z^*) is globally asymptotically stable; if $A_1A_2 < A_3$, from Poincaré-Bendixson Theorem then (x^*, y^*, z^*) is unstable with one dimensional stable manifold $W^s(x^*, y^*, z^*)$ such that the trajectory with

$$(x(0), y(0), z(0)) \notin W^s(x^*, y^*, z^*)$$

approaches a limit cycle Γ.

Remark 5.2 : Upper bounds and lower bounds of a periodic solutions $X(t)$, $Y(t)$, $Z(t)$.

We may improve the upper bound in (5.15) by introducing a lower bound of $X(t)$, $Y(t)$, and $Z(t)$. Since

$$X(t) \le \frac{\beta_1}{r_1} := X^{(1)}_{max},\ Y(t) \le \frac{\beta_2}{r_2} := Y^{(1)}_{max},\ Z(t) \le \frac{\beta_3}{r_3} := Z^{(1)}_{max}.$$

From the differential inequalities,

$$\begin{aligned}
\frac{dX}{dt} &\ge \beta_1 h_2\left(\frac{\beta_2}{r_2}\right) - r_1 X,\\
\frac{dY}{dt} &\ge \beta_2 h_3\left(\frac{\beta_3}{r_3}\right) - r_2 Y,\\
\frac{dZ}{dt} &\ge \beta_3 h_1\left(\frac{\beta_1}{r_1}\right) - r_3 Z,
\end{aligned}$$

We obtain lower bounds,

$$\begin{aligned}
X(t) &\ge \frac{\beta_1}{r_1} h_2\left(\frac{\beta_2}{r_2}\right) := X^{(1)}_{min},\\
Y(t) &\ge \frac{\beta_2}{r_2} h_3\left(\frac{\beta_3}{r_3}\right) := Y^{(1)}_{min},\\
Z(t) &\ge \frac{\beta_3}{r_3} h_1\left(\frac{\beta_1}{r_1}\right) := Z^{(1)}_{min}.
\end{aligned} \tag{5.17}$$

Using the lower bounds in (5.17), we improve the upper bounds in (5.14). From the differential inequalities,

$$\begin{aligned}
\frac{dX}{dt} &= \beta_1 h_2(Y) - r_1 X \le \beta_1 h_2\left(\frac{\beta_2}{r_2} h_3\left(\frac{\beta_3}{r_3}\right)\right) - r_1 X,\\
\frac{dY}{dt} &= \beta_2 h_3(Z) - r_2 Y \le \beta_2 h_3\left(\frac{\beta_3}{r_3} h_1\left(\frac{\beta_1}{r_1}\right)\right) - r_2 Y,\\
\frac{dZ}{dt} &= \beta_3 h_1(X) - r_3 Z \le \beta_3 h_1\left(\frac{\beta_1}{r_1} h_2\left(\frac{\beta_2}{r_2}\right)\right) - r_3 Z.
\end{aligned}$$

We obtain upper bounds,

$$
\begin{aligned}
X(t) &\leq \frac{\beta_1}{r_1} h_2\left(\frac{\beta_2}{r_2} h_3\left(\frac{\beta_3}{r_3}\right)\right) := X_{max}^{(2)}, \\
Y(t) &\leq \frac{\beta_2}{r_2} h_3\left(\frac{\beta_3}{r_3} h_1\left(\frac{\beta_1}{r_1}\right)\right) := Y_{max}^{(2)}, \\
Z(t) &\leq \frac{\beta_3}{r_3} h_1\left(\frac{\beta_1}{r_1} h_2\left(\frac{\beta_2}{r_2}\right)\right) := Z_{max}^{(2)}.
\end{aligned}
$$

From the following algorithm below, we obtain a sequence of upper bounds and lower bounds,

$$
\begin{aligned}
X_{max}^{(i+1)} &= \frac{\beta_1}{r_1} h_2\left(Y_{min}^{i}\right), \\
Y_{max}^{(i+1)} &= \frac{\beta_2}{r_2} h_3\left(Z_{min}^{i}\right), \quad i = 1, 2, \ldots \\
Z_{max}^{(i+1)} &= \frac{\beta_3}{r_3} h_1\left(X_{min}^{i}\right).
\end{aligned}
$$

$$
\begin{aligned}
X_{min}^{(i)} &= \frac{\beta_1}{r_1} h_2\left(Y_{max}^{(i)}\right), \\
Y_{min}^{(i)} &= \frac{\beta_2}{r_2} h_3\left(Z_{max}^{(i)}\right), \quad i = 1, 2, \ldots \\
Z_{min}^{(i)} &= \frac{\beta_3}{r_3} h_1\left(X_{max}^{(i)}\right).
\end{aligned}
$$

$\left\{X_{max}^{(i)}\right\}_{i=1}^{\infty}$ is a decreasing sequence and $\left\{X_{min}^{(i)}\right\}_{i=1}^{\infty}$ is an increasing sequence. Similarly, $\left\{Y_{max}^{(i)}\right\}_{i=1}^{\infty}$, $\left\{Z_{max}^{(i)}\right\}_{i=1}^{\infty}$ are decreasing sequences and $\left\{Y_{min}^{(i)}\right\}_{i=1}^{\infty}$, $\left\{Z_{min}^{(i)}\right\}_{i=1}^{\infty}$ are increasing sequences. We can improve the condition (H1) by

$$
\frac{n_1\left(X_{max}^{(i)}\right)^{n_1}}{\kappa_1^{n_1}+\left(X_{max}^{(i)}\right)^{n_1}} \frac{n_2\left(Y_{max}^{(i)}\right)^{n_2}}{\kappa_2^{n_2}+\left(Y_{max}^{(i)}\right)^{n_2}} \frac{n_3\left(Z_{max}^{(i)}\right)^{n_3}}{\kappa_3^{n_3}+\left(Z_{max}^{(i)}\right)^{n_3}} \leq 8,\ i = 1, 2, \ldots \qquad (\widehat{\mathrm{H}}1).
$$

Proof of Theorem 3.2 :

(i) For the Model $M2$, we first prove there exist a unique positive equilibrium (x^*, y^*, z^*) of the system (2.2). The positive equilibrium (x^*, y^*, z^*) satisfies

$$
\begin{aligned}
x &= \frac{\beta_1}{r_1 + r_{d1} g_2(y)} = G_2(y) \\
y &= \frac{\beta_2}{r_2 + r_{d2} g_3(z)} = G_3(z) \\
z &= \frac{\beta_3}{r_3 + r_{d3} g_1(x)} = G_1(x).
\end{aligned}
$$

The functions $G_1(x), G_2(y), G_3(z)$ are strictly decreasing. Then

$$
z = G_1(G_2(G_3(z))) = H(z),
$$

$H(0) > 0$, $H(z)$ is decreasing in z. Thus $z = H(z)$ has a unique positive solution z^*. Then $y^* = G_3(z^*)$, $x^* = G_2(y^*)$. The Jacobian of the system

(2.2) evaluated at (x^*, y^*, z^*) is

$$J(x^*, y^*, z^*) = \begin{bmatrix} -(r_1 + r_{d1}g_2(y^*)) & -r_{d1}g_2'(y^*)x^* & 0 \\ 0 & -(r_2 + r_{d2}g_3(z^*)) & -r_{d2}g_3'(z^*)y^* \\ r_{d3}g_1'(x^*)z^* & 0 & -(r_3 + r_{d3}g_1(x^*)) \end{bmatrix}.$$

The characteristic polynomial of $J(x^*, y^*, z^*)$ is

$$f(\lambda) = \lambda^3 + A_1\lambda^2 + A_2\lambda + A_3$$

where A_1, A_2, A_3 are listed in (3.2). Hence if, by Routh-Hurwitz criterion, $A_1A_2 > A_3$, then (a) holds. If $A_1A_2 < A_3$, then (b) holds.

(ii) Let F be the vector field of (2.2) and $(X(t), Y(t), Z(t))$ be a ω-periodic solution of the system (2.2). Then

$$DF(X, Y, Z) = \begin{bmatrix} -(r_1 + r_{d1}g_2(Y)) & -r_{d1}g_2'(Y)Z & 0 \\ 0 & -(r_2 + r_{d2}g_3(Z)) & -r_{d2}g_3'(Z)Y \\ r_{d3}g_1'(X)Z & 0 & -(r_3 + r_{d3}g_1(X)) \end{bmatrix}$$

and

$$DF^{[2]}(X, Y, Z) =$$

$$\begin{bmatrix} \begin{matrix} -(r_1 + r_{d1}g_2(Y)) \\ -(r_2 + r_{d2}g_3(Z)) \end{matrix} & -r_{d2}g_3'(Z)Y & 0 \\ 0 & \begin{matrix} -(r_1 + r_{d1}g_2(Y)) \\ -(r_3 + r_{d3}g_1(X)) \end{matrix} & -r_{d1}g_2'(Y)X \\ r_{d3}g_1'(X)Z & 0 & \begin{matrix} -(r_2 + r_{d2}g_3(Z)) \\ -(r_3 + r_{d3}g_1(X)) \end{matrix} \end{bmatrix}.$$

Consider ω-periodic linear equation

$$\frac{dU}{dt} = DF^{[2]}(X, Y, Z)U,\ U = (U_1, U_2, U_3). \tag{5.18}$$

As in the proof of Theorem 3.1, we introduce the function

$$W(X, Y, Z; U) = \sum_{i=1}^{3} p_i(X, Y, Z)|U_i|$$

and $W(t) = (X(t), Y(t), Z(t); U(t))$,

$$D_+W(t) = \sum_{i=1}^{3} p_i'(t)|U_i(t)| + p_i(t)D_+(|U_i(t)|).$$

Let

$$D1 = (r_1 + r_{d1}g_2(Y)) + (r_2 + r_{d2}g_3(Z))$$
$$D2 = (r_1 + r_{d1}g_2(Y)) + (r_3 + r_{d3}g_1(X))$$
$$D3 = (r_2 + r_{d2}g_3(Y)) + (r_3 + r_{d3}g_1(X)).$$

Since from (5.18)

$$\frac{dU_1}{dt} = (-D1)U_1 + (-r_{d2}g_3'(Z)Y)U_2$$
$$\frac{dU_2}{dt} = (-D2)U_2 + (-r_{d1}g_2'(Y)X)U_3$$
$$\frac{dU_3}{dt} = (-D3)U_3 + (-r_{d3}g_1'(X)Z)U_1.$$

Then

$$\begin{aligned}
D_+W(t) = &\left(\frac{p_1'}{p_1} + (-D1) + \frac{p_3}{p_1}(r_{d3}g_1'(X)Z)\right)p_1|U_1(t)| \\
&+ \left(\frac{p_2'}{p_2} + (-D2) + \frac{p_1}{p_2}(r_{d2}g_3'(Z)Y)\right)p_2|U_2(t)| \\
&+ \left(\frac{p_3'}{p_3} + (-D3) + \frac{p_2}{p_3}(r_{d1}g_2'(Y)X)\right)p_3|U_3(t)|.
\end{aligned}$$

From (2.2), we have

$$\begin{aligned}
\frac{1}{X}\frac{dX}{dt} &= \frac{\beta_1}{X} - (r_1 + r_{d1}g_2(Y)) \\
\frac{1}{Y}\frac{dY}{dt} &= \frac{\beta_2}{Y} - (r_2 + r_{d2}g_3(Z)) \\
\frac{1}{Z}\frac{dZ}{dt} &= \frac{\beta_3}{Z} - (r_3 + r_{d3}g_1(X)),
\end{aligned}$$

and

$$\begin{aligned}
\int_0^\omega \frac{\beta_1}{X} &= \int_0^\omega (r_1 + r_{d1}g_2(Y))dt \\
\int_0^\omega \frac{\beta_2}{Y} &= \int_0^\omega (r_2 + r_{d2}g_3(Z))dt \\
\int_0^\omega \frac{\beta_3}{Z} &= \int_0^\omega (r_3 + r_{d3}g_1(X))dt \\
\int_0^\omega D1 &= \int_0^\omega \frac{\beta_1}{X} + \frac{\beta_2}{Y} \\
\int_0^\omega D2 &= \int_0^\omega \frac{\beta_1}{X} + \frac{\beta_3}{Z} \\
\int_0^\omega D3 &= \int_0^\omega \frac{\beta_2}{Y} + \frac{\beta_3}{Z}.
\end{aligned}$$

Choose $p = p_3$, $p_1 = \dfrac{1}{p}$ such that

$$p^2 = \frac{\frac{\beta_1}{X} + \frac{\beta_2}{Y}}{r_{d3}g_1'(X)Z},$$

and

$$\begin{aligned}
\frac{\left(\frac{1}{p}\right)}{p_2}(r_{d2}g_3'(Z)Y) &\le \frac{\beta_1}{X} + \frac{\beta_3}{Z} \\
\frac{p_2}{p}(r_{d1}g_2'(Y)X) &\le \frac{\beta_2}{Y} + \frac{\beta_3}{Z}.
\end{aligned}$$

We need

$$\frac{r_{d3}g_1'(X)Z}{\frac{\beta_1}{X} + \frac{\beta_2}{Y}} = \frac{1}{p^2} \le \frac{\frac{\beta_1}{X} + \frac{\beta_3}{Z}}{r_{d2}g_3'(Z)Y}\,\frac{\frac{\beta_2}{Y} + \frac{\beta_3}{Z}}{r_{d1}g_2'(Y)X}$$

or

$$\begin{aligned} & r_{d1}g_2'(Y)X \cdot r_{d2}g_3'(Z)Y \cdot r_{d3}g_1'(X)Z \\ & \leq \left(\frac{\beta_1}{X}+\frac{\beta_2}{Y}\right)\left(\frac{\beta_1}{X}+\frac{\beta_3}{Z}\right)\left(\frac{\beta_3}{Z}+\frac{\beta_2}{Y}\right). \end{aligned} \tag{5.19}$$

It suffices to prove

$$r_{d1}r_{d2}r_{d3}\frac{n_1\kappa_1^{n_1}X^{n_1-1}}{(\kappa_1^{n_1}+X^{n_1})^2}\frac{n_2\kappa_2^{n_2}Y^{n_2-1}}{(\kappa_2^{n_2}+Y^{n_2})^2}\frac{n_3\kappa_3^{n_3}Z^{n_3-1}}{(\kappa_3^{n_3}+Z^{n_3})^2} \leq 8\cdot\frac{\beta_1\beta_2\beta_3}{X^2Y^2Z^2}. \tag{5.20}$$

If $n_1 = n_2 = n_3 = 1$ and

$$r_{d1}r_{d2}r_{d3}\frac{\kappa_1\kappa_2\kappa_3}{\beta_1\beta_2\beta_3} \leq 8, \tag{H2}$$

then (H2) implies (5.19) and every positive periodic solution is orbitally asymptotically stable.

Lemma 5.1 : *For each $n_i > 1$, $i = 1, 2, 3$,*

$$\max_{w>0} g_i'(w)w^2 = \max_{w>0}\frac{n_i\kappa_i^{n_i}w^{n_i+1}}{\left(\kappa_i^{n_i}+w^{n_i}\right)^2} = \frac{\kappa_i(n_i+1)(n_i-1)\sqrt[n_i]{\dfrac{n_i+1}{n_i-1}}}{4n_i}.$$

Proof. Let

$$f(w) = \frac{w^{n+1}}{\left(\kappa^n+w^n\right)^2}.$$

Then $f(0) = 0$ and $\lim_{w\to\infty} f(w) = 0$. Since

$$f'(w) = \frac{\left(\kappa^n+w^n\right)^2(n+1)w^n - 2w^{2n}n\left(\kappa^n+w^n\right)}{\left(\kappa^n+w^n\right)^4},$$

if $f'(w) = 0$ then $w^n = \left(\dfrac{n+1}{n-1}\right)\kappa^n$ and

$$\max_{w>0} f(w) = \frac{\dfrac{n+1}{n-1}\kappa\sqrt[n]{\dfrac{n+1}{n-1}}}{\kappa^n\left(\dfrac{2n}{n-1}\right)^2}.$$

Hence

$$\max_{w>0} g_i'(w)w^2 = \frac{\kappa_i(n_i+1)(n_i-1)\sqrt[n_i]{\dfrac{n_i+1}{n_i-1}}}{4n_i}.$$

□

Let

$$\frac{r_{d1}r_{d2}r_{d3}}{\beta_1\beta_2\beta_3}\prod_{i=1}^{3}\frac{\kappa_i(n_i+1)(n_i-1)\sqrt[n_i]{\dfrac{n_i+1}{n_i-1}}}{4n_i} \leq 8. \tag{H3}$$

For $n_i > 1$, $i = 1, 2, 3$, then from Lemma 5.1, (H3) implies (5.20) and every positive periodic solution is orbitally asymptotically stable. If $n_1 = n_2 = n_3 = 2$, then (H3) implies

$$\frac{r_{d_1} r_{d_2} r_{d_3}}{\beta_1 \beta_2 \beta_3} \cdot \frac{3\sqrt{3}}{8}\kappa_1 \frac{3\sqrt{3}}{8}\kappa_2 \frac{3\sqrt{3}}{8}\kappa_3 \leq 8.$$

From the system (2.2) we obtain differential inequalities

$$\frac{dx}{dt} \leq \beta_1 - r_1 x,\ \frac{dy}{dt} \leq \beta_2 - r_2 y,\ \frac{dz}{dt} \leq \beta_3 - r_3 z.$$

Under the assumption (H2) or (H3), similarly as in the proof of Theorem 3.1 (ii), we complete the proof of Theorem 3.2 (ii).

Proof of Theorem 3.3 :

(i) For the Model $M3$, from the hypothesis ($\widehat{\text{M}}3$) we prove there exists a unique positive equilibrium (x^*, y^*, z^*) by solving

$$x = K^{-1}(\beta_1 h_2(y)) = G_2(y)$$

where $K(x) = r_1 x - \beta_p g_1(x) > 0$, $K'(x) > 0$ for $x > 0$, K^{-1} is the inverse of $K(x)$, and

$$\begin{aligned} y &= \frac{\beta_2}{r_2} h_3(z) = G_3(z) \\ z &= \frac{\beta_3}{r_3} h_1(x) = G_1(x). \end{aligned}$$

The functions $G_1(x)$, $G_2(y)$, and $G_3(z)$ are strictly decreasing. We note that

$$G_2'(y) = (K^{-1})'(\beta_1 h_2(y))\beta_1 h_2'(y) < 0.$$

Then $z = G_1(G_2(G_3(z))) = H(z)$, $H(0) > 0$, and $H(z)$ is decreasing in z. Thus $z = H(z)$ has a unique positive solution z^*. Then $y^* = G_3(z^*)$, $x^* = G_2(y^*)$. The Jacobian of the system (2.3) evaluated at (x^*, y^*, z^*) is

$$J = \begin{bmatrix} \beta_p g_1'(x^*) - r_1 & \beta_1 h_2'(y^*) & 0 \\ 0 & -r_2 & \beta_2 h_3'(z^*) \\ \beta_3 h_1'(x^*) & 0 & -r_3 \end{bmatrix}.$$

The characteristic polynomial of $J(x^*, y^*, z^*)$ is

$$f(\lambda) = \lambda^3 + A_1 \lambda^2 + A_2 \lambda + A_3$$

where A_1, A_2, and A_3 are listed in (3.3). Hence by Routh-Hurwitz criterion if $A_1 A_2 > A_3$, then (a) holds. If $A_1 A_2 < A_3$ then (b) holds. We note that if $r_1 - \beta_p g_1'(x^*) > 0$, then A_1, A_2, $A_3 > 0$.

(ii) Under the additional assumption ($\widehat{\text{M}}3$), we have

$$r_1 - \beta_p g_1'(x) > 0.$$

From the system (2.3) we obtain differential inequalities

$$\frac{dx}{dt} \leq \beta_1 + \beta_p - r_1 x,\ \frac{dy}{dt} \leq \beta_2 - r_2 y,\ \frac{dz}{dt} \leq \beta_3 - r_3 z.$$

Under the assumption (H4), similarly as in the proof of Theorem 3.1 (ii), we complete the proof of Theorem 3.3 (ii) by replacing r_1 by $r_1 - \beta_p g_1'(x)$ in (5.7), (5.8), replacing $r_1 X$ by $r_1 X - \beta_p g_1(X)$ in (5.9), (5.10) and replacing $\dfrac{\beta_1}{r_1}$ by $\dfrac{\beta_1 + \beta_p}{r_1}$ in (5.16).

Proof of Theorem 3.4 :

(i) For the Model $M4$, we prove there exists a unique positive equilibrium (x^*, y^*, z^*) by solving

$$z = \frac{\beta_3}{r_3 + r_{d3} g_1(x)} = G_1(x),\ G_1'(x) < 0$$
$$y = \frac{\beta_2}{r_2 + r_{d2} g_3(z)} = G_3(z),\ G_3'(z) < 0.$$

Let

$$K(x) = \frac{\beta_1 + \beta_p g_1(x)}{x}.$$

Then

$$K'(x) = \frac{x\beta_p g_1'(x) - (\beta_1 + \beta_p g_1(x))}{x^2},$$

and

$$K'(x) < 0 \iff x g_1'(x) - g_1(x) < \frac{\beta_1}{\beta_p}.$$

Since

$$\begin{aligned} x g_1'(x) - g_1(x) &= \frac{x^{n_1}}{(\kappa^{n_1} + x^{n_1})^2}\left[x n_1 \kappa^{n_1} - (\kappa^{n_1} + x^{n_1})\right] \\ &= \frac{x^{n_1}}{(\kappa^{n_1} + x^{n_1})^2}\psi(x), \end{aligned}$$

$$\psi'(x) = 0 \iff \kappa^{n_1} x^{n_1 - 1} \text{ or } x = \kappa^{\frac{n_1}{n_1 - 1}}.$$

Then there exists $\widetilde{x}_1$, $\widetilde{x}_2$, $0 < \widetilde{x}_1 < \widetilde{x}_2$ such that

$$\psi(x) < 0 \text{ for } 0 < x < \widetilde{x}_1 \text{ or } x > \widetilde{x}_2,$$

and

$$\psi(x) > 0 \text{ for } \widetilde{x}_1 < x < \widetilde{x}_2.$$

Thus for $\beta_p > 0$ small such that

$$\max_{\widetilde{x}_1 \le x \le \widetilde{x}_2} (x g_1'(x) - g_1(x)) < \frac{\beta_1}{\beta_p}.$$

From assumption ($\widehat{\mathrm{M}}4$), $K'(x) < 0$ for all $x > 0$, We have $K(x) = r_1 + r_{d1} g_2(y)$, and

$$x = K^{-1}(r_1 + r_{d1} g_2(y)) = G_2(y),\ G_2'(y) < 0 \text{ for } y > 0.$$

Hence there exists a unique positive equilibrium (x^*, y^*, z^*). The Jacobian of the system (2.4) evaluated at (x^*, y^*, z^*) is

$$J(x^*, y^*, z^*) =$$
$$\begin{bmatrix} -(r_1 + r_{d1} g_2(y^*)) + \beta_p g_1'(x^*) & -r_{d1} g_2'(y^*) x^* & 0 \\ 0 & -(r_2 + r_{d2} g_3(z^*)) & -r_{d2} g_3'(z^*) y^* \\ -r_{d3} g_1'(x^*) z^* & 0 & -(r_3 + r_{d3} g_1(x^*)) \end{bmatrix}.$$

The characteristic polynomial of $J(x^*, y^*, z^*)$ is

$$f(\lambda) = \lambda^3 + A_1 \lambda^2 + A_2 \lambda + A_3$$

where A_1, A_2, A_3 are listed in (3.4). As in the proof of Theorem 3.1, we complete the proof of Theorem 3.4 (i).

(ii) Let $(X(t), Y(t), Z(t))$ be a ω-periodic solution of (2.4). As in the proof of Theorem 3.1 (ii). Then

$$DF(X,Y,Z) =$$

$$\begin{bmatrix} -(r_1 + r_{d1}g_2(Y)) + \beta_p g_1'(X) & -r_{d1}g_2'(Y)X & 0 \\ 0 & -(r_2 + r_{d2}g_3(Z)) & -r_{d2}g_3'(Z)Y \\ -r_{d3}g_1'(X)Z & 0 & -(r_3 + r_{d3}g_1(X)) \end{bmatrix},$$

and

$$DF^{[2]}(X,Y,Z) =$$

$$\begin{bmatrix} \begin{array}{l} -(r_1 + r_{d1}g_2(Y)) + \beta_p g_1'(X) \\ -(r_2 + r_{d2}g_3(Z)) \end{array} & -r_{d2}g_3'(Z)Y & 0 \\ 0 & \begin{array}{l} -(r_1 + r_{d1}g_2(Y)) + \beta_p g_1'(X) \\ -(r_3 + r_{d3}g_1(X)) \end{array} & -r_{d1}g_2'(Y)X \\ r_{d3}g_1(X)Z & 0 & \begin{array}{l} -(r_2 + r_{d2}g_3(Z)) \\ -(r_3 + r_{d3}g_1(X)) \end{array} \end{bmatrix}.$$

As in proof of Theorem 3.2 for Model $M2$, we replace

$$D1 \text{ by } (r_1 + r_{d1}g_2(Y)) + (r_2 + r_{d2}g_3(Z)) - \beta_p g_1'(X)$$
$$D2 \text{ by } (r_1 + r_{d1}g_2(Y)) + (r_3 + r_{d3}g_1(X)) - \beta_p g_1'(X),$$

and keep $D3$ in the same

$$D3 = (r_2 + r_{d2}g_3(Z)) + (r_3 + r_{d3}g_1(X)).$$

From (3.4)

$$\begin{aligned} \frac{1}{X}\frac{dX}{dt} &= \frac{\beta_1}{X} + \beta_p \frac{g_1(X)}{X} - (r_1 + r_{d1}g_2(Y)) \\ \frac{1}{Y}\frac{dY}{dt} &= \frac{\beta_2}{Y} - (r_2 + r_{d2}g_3(Z)) \\ \frac{1}{Z}\frac{dZ}{dt} &= \frac{\beta_3}{Z} - (r_3 + r_{d3}g_1(X)). \end{aligned}$$

As in the proof of Theorem 3.2, we choose $p_3 = p$, $p_1 = \frac{1}{p}$ such that

$$\begin{aligned} &\int_0^\omega (-D1) + \frac{p_3}{p_1} r_{d3}g_1'(X)Z \le 0 \\ &\int_0^\omega (-D2) + \frac{p_1}{p_2} r_{d2}g_3'(Z)Y \le 0 \\ &\int_0^\omega (-D3) + \frac{p_2}{p_3} r_{d1}g_2'(Y)X \le 0. \end{aligned}$$

Choose

$$p = \sqrt{\frac{\frac{\beta_1}{X} + \beta_p \frac{g_1(X)}{X} + \frac{\beta_2}{Y}}{r_{d2}g_3'(Z)Y}},$$

and p_2 such that

$$\frac{r_{d1}g_2'(Y)X}{\frac{\beta_3}{Z} + \frac{\beta_2}{Y}} \le \frac{p_3}{p_2} \le \frac{\left(\frac{\beta_1}{X} + \beta_p \frac{g_1(X)}{X} + \frac{\beta_2}{Y}\right)}{r_{d3}g_1'(X)Z} \frac{\left(\frac{\beta_1}{X} + \beta_p \frac{g_1(X)}{X} + \frac{\beta_3}{Z}\right)}{r_{d2}g_3'(Z)Y}.$$

We need

$$
\begin{aligned}
&(r_{d1}g_2'(Y)X)(r_{d2}g_3'(Z)Y)(r_{d3}g_1'(X)Z)\\
\leq &\left(\frac{\beta_1}{X}+\beta_p\frac{g_1(X)}{X}+\frac{\beta_2}{Y}\right)\left(\frac{\beta_1}{X}+\beta_p\frac{g_1(X)}{X}+\frac{\beta_3}{Z}\right)\left(\frac{\beta_3}{Z}+\frac{\beta_2}{Y}\right).
\end{aligned}
$$

Let

$$
A=\frac{\beta_1+\beta_p g_1(X)}{X},\ B=\frac{\beta_2}{Y},\ C=\frac{\beta_3}{Z}.
$$

Then

$$
\begin{aligned}
&(r_{d1}g_2'(Y)X)(r_{d2}g_3'(Z)Y)(r_{d3}g_1'(X)Z)\\
\leq&(A+B)(A+C)(B+C)\\
=&A^2C+A^2B+AB^2+ABC+AC^2+BC^2+B^2C+ABC.
\end{aligned}
$$

Apply the inequality,

$$
\frac{a_1+a_2+\cdots+a_n}{n}\geq\sqrt[n]{a_1a_2\dots a_n},
$$

whenever $a_i>0$, $i=1,2,\cdots,n$. We obtain

$$
A^2C+A^2B+AB^2+ABC+AC^2+BC^2+B^2C+ABC\geq 8\sqrt[8]{A^8B^8C^8}.
$$

It suffices to show

$$
(r_{d1}g_2'(Y)X)(r_{d2}g_3'(Z)Y)(r_{d3}g_1'(X)Z)\leq 8\left(\frac{\beta_1\beta_2\beta_3}{XYZ}+\frac{\beta_p g_1(X)\beta_2\beta_3}{XYZ}\right),
$$

or

$$
(r_{d1}g_2'(Y)Y^2)(r_{d2}g_3'(Z)Z^2)(r_{d3}g_1'(X)X^2)\leq 8\beta_2\beta_3(\beta_1+\beta_p g_1(X)). \tag{5.21}
$$

By Lemma 5.1, it suffices to show

$$
\prod_{i=1}^{3} r_{di}\frac{\kappa_i(n_i+1)(n_i-1)\sqrt[n_i]{\frac{n_i+1}{n_i-1}}}{4n_i}\leq 8\beta_1\beta_2(\beta_1+\beta_p g_1(x_{low})) \tag{H4}
$$

where x_{low} is the root of

$$
\beta_1+\beta_p g_1(X)=\left(r_1+r_{d1}g_2\left(\frac{\beta_2}{r_2}\right)\right)X.
$$

We note that x_{low} follow by the below inequality

$$
\begin{aligned}
\frac{dX}{dt}&=\beta_1+\beta_p g_1(X)-(r_1+r_{d1}g_2(Y))X\\
&\geq\beta_1+\beta_p g_1(X)-r_1X-r_{d1}g_2\left(\frac{\beta_2}{r_2}\right)X.
\end{aligned}
$$

From the system (2.4) we obtain differential inequalities

$$
\frac{dx}{dt}\leq\beta_1+\beta_p-r_1x,\ \frac{dy}{dt}\leq\beta_2-r_2y,\ \frac{dz}{dt}\leq\beta_3-r_3z.
$$

Since (H4) implies (5.21). Under the assumption (H4), similarly as in the proof of Theorem 3.1 (ii), we complete the proof of Theorem 3.4 (ii) by replacing $\dfrac{\beta_1}{r_1}$ by $\dfrac{\beta_1+\beta_p}{r_1}$ in (5.16).

Proof of Theorem 3.5 :

(i) For the Model $M5$, we prove that there exists a unique positive equilibrium (x^*, y^*, z^*) by solving

$$\begin{aligned} x &= \frac{\beta_1 h_2(y)}{r_1 + r_{d1} g_2(y)} = G_2(y) \downarrow \text{ in } y \\ y &= \frac{\beta_2 h_3(z)}{r_2 + r_{d2} g_3(z)} = G_3(z) \downarrow \text{ in } z \\ z &= \frac{\beta_3 h_1(x)}{r_3 + r_{d3} g_1(x)} = G_1(x) \downarrow \text{ in } x. \end{aligned}$$

Hence we solve $z = G_1(G_2(G_3(z))) = H(z)$ is a strictly decreasing function with $H(0) > 0$. Hence the fixed point z^* is unique and the positive equilibrium (x^*, y^*, z^*) is unique. The Jacobian of the system (2.5) evaluated at (x^*, y^*, z^*) is

$$J(x^*, y^*, z^*) =$$
$$\begin{bmatrix} -(r_1 + r_{d1} g_2(y^*)) & \beta_1 h_2'(y^*) - r_{d1} g_2'(y^*) x^* & 0 \\ 0 & -(r_2 + r_{d2} g_3(z^*)) & \beta_3 h_3'(z^*) - r_{d2} g_3'(z^*) y^* \\ \beta_3 h_1'(x^*) - r_{d3} g_1'(x^*) z^* & 0 & -(r_3 + r_{d3} g_1(x^*)) \end{bmatrix}.$$

The characteristic polynomial of $J(x^*, y^*, z^*)$ is

$$f(\lambda) = \lambda^3 + A_1 \lambda^2 + A_2 \lambda + A_3.$$

where A_1, A_2, and A_3 are listed in (3.5). As in the proof of Theorem 3.1, we complete the proof of Theorem 3.5 (i).

(ii) Let $(X(t), Y(t), Z(t))$ be a ω-periodic solution of (2.5). As in the proof of Theorem 3.1 (ii),

$$DF(X, Y, Z) = \begin{bmatrix} -(r_1 + r_{d1} g_2(Y)) & \beta_1 h_2'(Y) - r_{d1} g_2'(Y) X & 0 \\ 0 & -(r_2 + r_{d2} g_3(Z)) & \beta_3 h_3'(X) - r_{d2} g_3'(Z) Y \\ \beta_3 h_1'(X) - r_{d3} g_1'(X) Z & 0 & -(r_3 + r_{d3} g_1(X)) \end{bmatrix},$$

and

$$DF^{[2]}(X, Y, Z) =$$
$$\begin{bmatrix} \begin{array}{c} -(r_1 + r_{d1} g_2(Y)) \\ -(r_2 + r_{d2} g_3(Z)) \end{array} & \beta_2 h_3'(Z) - r_{d2} g_3'(Z) Y & 0 \\ 0 & \begin{array}{c} -(r_1 + r_{d1} g_2(Y)) \\ -(r_3 + r_{d3} g_1(X)) \end{array} & \beta_1 h_2'(Y) - r_{d1} g_2'(Y) X \\ -(\beta_3 h_1'(X) - r_{d3} g_1'(X) Z) & 0 & \begin{array}{c} -(r_2 + r_{d2} g_3(Z)) \\ -(r_3 + r_{d3} g_1(X)) \end{array} \end{bmatrix}.$$

As in the proof of Theorem 3.1 for Model $M1$, we consider

$$\frac{dU}{dt} = DF^{[2]}(X, Y, Z) U$$

and introduce the function

$$W(X, Y, Z; U) = \sum_{i=1}^{3} p_i(X, Y, Z) |U_i|.$$

Let $W(t) = W(X(t), Y(t), Z(t)); U(t))$ and compute

$$
\begin{aligned}
&D_+W(t) = \sum_{i=1}^{3} p_i'(t)|U_i(t)| + p_i(t)D_+(|U_i(t)|) \\
&\le \left(\frac{p_1'(t)}{p_1(t)} - (r_1 + r_{d1}g_2(Y) + r_2 + r_{d2}g_3(Z)) + \frac{p_3(t)}{p_1(t)}(-\beta_3 h_1'(X) + r_{d3}g_1'(X)Z)\right) p_1(t)|U_1(t)| \\
&+ \left(\frac{p_2'(t)}{p_2(t)} - (r_1 + r_{d1}g_2(Y) + r_3 + r_{d3}g_1(X)) + \frac{p_1(t)}{p_2(t)}(-\beta_2 h_3'(Z) + r_{d2}g_3'(Z)Y)\right) p_2(t)|U_2(t)| \\
&+ \left(\frac{p_3'(t)}{p_3(t)} - (r_2 + r_{d2}g_3(Z) + r_3 + r_{d3}g_1(X)) + \frac{p_2(t)}{p_3(t)}(-\beta_1 h_2'(Y) + r_{d1}g_2'(Y)X)\right) p_3(t)|U_3(t)|.
\end{aligned}
$$

Since

$$
\begin{aligned}
\frac{1}{X}\frac{dX}{dt} &= \frac{\beta_1 h_2(Y)}{X} - (r_1 + r_{d1}g_2(Y)) \\
\frac{1}{Y}\frac{dY}{dt} &= \frac{\beta_2 h_3(Z)}{Y} - (r_2 + r_{d2}g_3(Z)) \\
\frac{1}{Z}\frac{dZ}{dt} &= \frac{\beta_3 h_1(X)}{Z} - (r_3 + r_{d3}g_1(X)),
\end{aligned}
$$

we need

$$
\begin{aligned}
\frac{p_3(t)}{p_1(t)}(-\beta_3 h_1'(X) + r_{d3}g_1'(X)Z) &\le \frac{\beta_1 h_2(Y)}{X} + \frac{\beta_2 h_3(Z)}{Y} \\
\frac{p_1(t)}{p_2(t)}(-\beta_2 h_3'(Z) + r_{d2}g_3'(Z)Y) &\le \frac{\beta_1 h_2(Y)}{X} + \frac{\beta_3 h_1(X)}{Z} \\
\frac{p_2(t)}{p_3(t)}(-\beta_1 h_2'(Y) + r_{d1}g_2'(Y)X) &\le \frac{\beta_2 h_3(Z)}{Y} + \frac{\beta_3 h_1(X)}{Z}.
\end{aligned}
$$

Choose $p_3 = p$, $p_1 = \dfrac{1}{p}$,

$$
p = \sqrt{\frac{\dfrac{\beta_1 h_2(Y)}{X} + \dfrac{\beta_2 h_3(Z)}{Y}}{-\beta_3 h_1'(X) + r_{d3}g_1'(X)Z}}.
$$

We need

$$
\frac{-\beta_1 h_2'(Y) + r_{d1}g_2'(Y)X}{\dfrac{\beta_2 h_3(Z)}{Y} + \dfrac{\beta_3 h_1(X)}{Z}} \le \frac{p_3}{p_2} \le \frac{\dfrac{\beta_1 h_2(Y)}{X} + \dfrac{\beta_2 h_3(Z)}{Y}}{-\beta_3 h_1'(X) + r_{d3}g_1'(X)Z} \cdot \frac{\dfrac{\beta_1 h_2(Y)}{X} + \dfrac{\beta_3 h_1(X)}{Z}}{-\beta_2 h_3'(Z) + r_{d2}g_3'(Z)Y}.
$$

or

$$
\begin{aligned}
&(-\beta_1 h_2'(Y) + r_{d1}g_2'(Y)X)(-\beta_3 h_1'(X) + r_{d3}g_1'(X)Z)(-\beta_2 h_3'(Z) + r_{d2}g_3'(Z)Y) \\
&\le \left(\frac{\beta_2 h_3(Z)}{Y} + \frac{\beta_3 h_1(X)}{Z}\right)\left(\frac{\beta_1 h_2(Y)}{X} + \frac{\beta_2 h_3(Z)}{Y}\right)\left(\frac{\beta_1 h_2(Y)}{X} + \frac{\beta_3 h_1(X)}{Z}\right).
\end{aligned}
$$

It suffices to show

$$
\begin{aligned}
&(-\beta_1 h_2'(Y) + r_{d1}g_2'(Y)X)(-\beta_3 h_1'(X) + r_{d3}g_1'(X)Z)(-\beta_2 h_3'(Z) + r_{d2}g_3'(Z)Y) \\
&\le 8\,\frac{\beta_1\beta_2\beta_3 h_1(X)h_2(Y)h_3(Z)}{XYZ}.
\end{aligned}
\tag{5.22}
$$

Let

$$\begin{aligned} h_i(w) &= \frac{\kappa_i^{n_i}}{\kappa_i^{n_i} + w^{n_i}},\ h_i(0) = 1, \\ h_i'(w) &= \frac{-\kappa_i^{n_i} n_i w^{n_i-1}}{(\kappa_i^{n_i} + w^{n_i})^2}, \\ g_i(w) &= \frac{w^{n_i}}{\kappa_i^{n_i} + w^{n_i}}, \\ g_i'(w) &= \frac{\kappa_i^{n_i} n_i w^{n_i-1}}{(\kappa_i^{n_i} + w^{n_i})^2}, \end{aligned} \tag{5.23}$$

for $i = 1, 2, 3$. Substituting (5.23) into (5.22) yields

$$\begin{aligned} 8\beta_1\beta_2\beta_3\kappa_1^{n_1}\kappa_2^{n_2}\kappa_3^{n_3} \geq & \left(\beta_1 \frac{\kappa_2^{n_2} n_2 Y^{n_2}}{\kappa_2^{n_2} + Y^{n_2}} + \frac{r_{d1}\kappa_2^{n_2} n_2 Y^{n_2}}{\kappa_2^{n_2} + Y^{n_2}} X\right) \\ & \cdot \left(\beta_3 \frac{\kappa_1^{n_1} n_1 X^{n_1}}{\kappa_1^{n_1} + X^{n_1}} + \frac{r_{d3}\kappa_1^{n_1} n_1 X^{n_1}}{\kappa_1^{n_1} + X^{n_1}} Z\right) \\ & \cdot \left(\beta_2 \frac{\kappa_3^{n_3} n_3 Z^{n_3}}{\kappa_3^{n_3} + Z^{n_3}} + \frac{r_{d2}\kappa_3^{n_3} n_3 Z^{n_3}}{\kappa_3^{n_3} + Z^{n_3}} Y\right) \end{aligned} \tag{5.24}$$

Since

$$\begin{aligned} \frac{dX}{dt} &= \beta_1 h_2(Y) - (r_1 + r_{d1} g_2(Y))X \\ &\leq \beta_1 h_2(0) - (r_1 + r_{d1} \cdot 0)X \\ &= \beta_1 - r_1 X. \end{aligned}$$

Hence $X(t) \leq \frac{\beta_1}{r_1}$. Similarly $Y(t) \leq \frac{\beta_2}{r_2}$ and $Z(t) \leq \frac{\beta_3}{r_3}$. Let

$$\begin{aligned} 8\beta_1\beta_2\beta_3 \geq & \left(n_2 g_2\left(\frac{\beta_2}{r_2}\right)\right)\left(\beta_1 + r_{d1}\frac{\beta_1}{r_1}\right) \\ & \cdot \left(n_1 g_1\left(\frac{\beta_1}{r_1}\right)\right)\left(\beta_3 + r_{d3}\frac{\beta_3}{r_3}\right) \\ & \cdot \left(n_3 g_3\left(\frac{\beta_3}{r_3}\right)\right)\left(\beta_2 + r_{d2}\frac{\beta_2}{r_2}\right) \end{aligned} \tag{H5}$$

be (H5). Then (H5) implies (5.24). Let

$$8 \geq \left(1 + \frac{r_{d1}}{r_1}\right) n_2 \cdot \left(1 + \frac{r_{d3}}{r_3}\right) n_1 \cdot \left(1 + \frac{r_{d2}}{r_2}\right) n_3. \tag{H6}$$

Then (H6) implies (H5). From the system (2.5) we obtain differential inequalities

$$\frac{dx}{dt} \leq \beta_1 - r_1 x,\ \frac{dy}{dt} \leq \beta_2 - r_2 y,\ \frac{dz}{dt} \leq \beta_3 - r_3 z.$$

Under the assumption (H5), similarly as in the proof of Theorem 3.1 (ii), we complete the proof of Theorem 3.5 (ii).

Conflict of Interest. No competing interests need to be declared for two authors.

Acknowledgments. C.P.Hsu acknowledges support from Academia Sinica and the Ministry of Science and Technology of Taiwan (MOST 110-2123-M-001-005 and 111-2123-M-001-003-), and S. B. Hsu is supported by MOST 109-2115-M-007-005. Both of us acknowledge Yu-Chuan Chen for his help in numerical test.

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Received July 2022; revised November 2022; early access December 2022.