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ASYMPTOTIC PROPERTIES OF MOLECULAR MECHANISM MODELS WITH FUNCTIONAL RESPONSE

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Abstract. In this study, several modified types of the Goodwin model are proposed to demonstrate oscillatory behaviors. The original Goodwind model is the prototype model of a negative feedback loop that exhibits oscillations. But it exhibits oscillations when the cooperativity is very high, $n > 8$, which is unrealistic in most biological situations. We show two cases of a modified Goodwin model with functional responses of order $n = 5$ and $n = 6$ which exhibit periodic oscillations. It is shown that the modified functional responses lead to produce oscillatory solutions in these cases. This result suggests the possibility of constructing models to have oscillatory solutions with lower order functional responses than the requirement $n > 8$ for the original Goodwin model case.

Keywords: Goodwin model; functional response; negative feedback loop; oscillatory solution.
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1. Introduction

Constructing and analyzing mathematical models that can reproduce various oscillation phenomena has been an important topic in biology and chemistry. The Goodwin model has been proposed by B. Goodwin in 1965 in the work titled "Oscillatory behavior in enzymatic control process"[6]. This is the prototype model of a negative feedback loop that exhibits oscillatory behavior.

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In the scheme of the Goodwin model a genetic locus produces a type of mRNA (X). This mRNA then produces a protein (Y), and this protein then undergoes a metabolic process to produce another protein (Z), which acts as an inhibitor of mRNA (X) production. The inhibitor role is represented by the negative feedback loop in which protein Z exerts its influence on transcription via a Hill function.

The Goodwin model reflecting this scheme is expressed as the following system of differential equations.

$$\begin{cases} \dfrac{dX}{dt} = k_1 \dfrac{K^n}{K^n + Z^n} - k_2 X \\ \dfrac{dY}{dt} = k_3 X - k_4 Y \\ \dfrac{dZ}{dt} = k_5 Y - k_6 Z \end{cases} \tag{1}$$

where $k_1, k_2, k_3, k_4, k_5, k_6, K, n$ are positive parameters.

This negative feedback loops may produce periodic oscillations for $n > 8$ as shown in Figure 6 in Section 3. For $n < 8$ the oscillations are always dampened as shown in Figures 4 and 5 in Section 3. Griffiths[7] showed in 1968 that limit cycle oscillations are possible to arise only if the Hill coefficient n is greater than 8 in the Goodwin model. For $n \leq 8$, the Goodwin model exhibits damped oscillations as shown in [18].

The Goodwin model is the first to demonstrate oscillations at the molecular level. Oscillations in molecular biological systems are widely reported and mathematically investigated[8, 9, 17]. The Goodwin has since been applied in the context of circadian clocks[3, 4, 10, 13, 15]. Also, the Goodwin model has been used in a variety of research fields, including somitogenesis[19], gene circuit modeling[1], and cell cycle with functional response[2]. In particular, a modification of the Goodwin model that replaces the Hill type function by an arbitrary two-threshold reset function[11, 12, 14] has been used to regenerate phase curves and study temperature compensation in circadian systems.

The Hill coefficient n indicates the degree of cooperativity, that is, for example related to genomics, how many regulator Z molecules bind to a promoter. The Goodwin model has been criticized for exhibiting oscillations when the cooperativity is very high, $n > 8$, which is unrealistic in most biological situations. There are recent studies that attempt to lower the cooperative order requirement to obtain oscillatory behavior, for example by adding phosphorylation and dephosphorylation processes, as noted in the study by Gonze and Abou-Jaoude[5].

In this paper we examine periodic oscillations for the following model which is a modified form of Goodwin model.

$$\begin{cases} \dfrac{dX}{dt} = k_1 \dfrac{K^n}{K^n - aZ^{n-1} + Z^n} - k_2 X \\ \dfrac{dY}{dt} = k_3 X - k_4 Y \\ \dfrac{dZ}{dt} = k_5 Y - k_6 Z \end{cases} \tag{2}$$

where the parameters $k_1, k_2, k_3, k_4, k_5, k_6, K, a$ are positive and $n \geq 1$.
It is shown in Section 3 that periodic oscillations may appear for system (2) with functional responses of order $n = 5$, $n = 6$ which are lower than the order requirement $n > 8$ for the original Goodwin model case.

We would analyze the following two example cases for the modified Goodwin model (2) to analyze asymptotic properties in detail.

Case 1. $n = 5$ and $k_1 = k_3 = k_5 = 1$, $k_2 = k_4 = k_6 = 0.1$, $K = 1$:

$$\begin{cases} \dfrac{dX}{dt} = \dfrac{1}{1 - 3Z^4 + Z^5} - (0.1)X \\ \dfrac{dY}{dt} = X - (0.1)Y \\ \dfrac{dZ}{dt} = Y - (0.1)Z \end{cases} \tag{3}$$

Case 2. $n = 6$ and $k_1 = k_3 = k_5 = 1$, $k_2 = k_4 = k_6 = 0.1$, $K = 1$:

$$\begin{cases} \dfrac{dX}{dt} = \dfrac{1}{1 - 2Z^5 + Z^6} - (0.1)X \\ \dfrac{dY}{dt} = X - (0.1)Y \\ \dfrac{dZ}{dt} = Y - (0.1)Z \end{cases} \tag{4}$$

In Section 2 we analyze the existence and stability of a unique positive constant steady-state for the system (3) and (4). Limit cycle phenomena around the unique positive steady-states of the system (3) and (4) are presented by numerical simulations in Section 3. Also in Section 3, it is shown that the corresponding types of the orginal Goodwin model do not display limit cycles. Finally, the conclusion is stated in Section 4.

2. Stability of Constant Steady-States for the Modified Goodwin Model

In the modified Goodwin model (2) the right-hand side of each equations are continuous functions of the variables X, Y, Z, so the local existence of the solution to the system of differential equations (2) is guaranteed. The positivity and boundedness of the solution to the system (2) are examined in the following Lemma.

Lemma 1. *Every trajectory of the solution* $(X(t),Y(t),Z(t))$ *of the system* (2) *stays in a bounded closed region in* $\Omega = \{(X,Y,Z) \mid X>0, Y>0, Z>0\}$ *for all* $t \geq 0$ *if*

$$0 < \frac{K^n}{K^n - aZ^{n-1} + Z^n} < 1 \quad \textit{for all } t \geq 0.$$

Proof. We assume positive initial conditions:

$$X(0) > 0, \quad Y(0) > 0, \quad Z(0) > 0.$$

From the equation for X in the system (2) with the given condition we have the inequalities

$$0 < \frac{dX}{dt} + k_2 X = k_1 \frac{K^n}{K^n - aZ + Z^n} < k_1.$$

Let $u(t) = e^{k_2 t} X(t)$. Then

$$0 < u'(t) = e^{k_2 t}\left(X'(t) + k_2 X(t)\right) \leq k_1 e^{k_2 t}$$

$$0 \leq \int_0^t u'(s)\,ds \leq k_1 \int_0^t e^{k_2 s}\,ds$$

$$u(0) \leq u(t) \leq u(0) + k_1 \int_0^t e^{k_2 s}\,ds$$

Since $u(0) = X(0)$, we obtain

$$\begin{aligned} X(0)e^{-k_2 t} \;\leq\; X(t) \;&\leq\; X(0)e^{-k_2 t} + k_1 \textstyle\int_0^t e^{k_2(s-t)}\,ds \\ &= X(0)e^{-k_2 t} + \frac{k_1}{k_2}\left(1 - e^{-k_2 t}\right) \\ &\leq X(0) + \frac{k_1}{k_2} \end{aligned}$$

Thus $X(t)$ remains positive and bounded by a constant $M_1 = X(0) + \frac{k_1}{k_2}$.

Similarily as the case of $X(t)$, it is shown that $Y(t)$ and $Z(t)$ are also positive and bounded. Thus we conclude that the solution $(X(t), Y(t), Z(t))$ of the system (2) stays in a bounded closed region in $\Omega = \{(X,Y,Z) \mid X > 0, Y > 0, Z > 0\}$ for all $t \geq 0$. $\square$

Now in Theorem 1 and 2 we find positive constant equilibrium points and analyze the stability in Case 1 and 2, respectively.

Theorem 1. *In Case 1 the system* (3) *possesses a unique positive constant steady-state* $\left(\overline{X}, \overline{Y}, \overline{Z}\right) \approx (0.03988, 0.3988, 3.988)$ *which is unstable.*

Proof. Steady-states of the system (3) are the solutions of

$$\frac{dX}{dt} = \frac{dY}{dt} = \frac{dZ}{dt} = 0$$

that is

$$\begin{cases} \dfrac{1}{1 - 3Z^4 + Z^5} - (0.1)X = 0 \\ X - (0.1)Y = 0 \\ Y - (0.1)Z = 0. \end{cases}$$

From last two equations

$$X = (0.1)Y = (0.1)^2 Z.$$

and thus the first equation is reduced to

$$f(Z) = (0.1)X = (0.1)^3 Z \tag{5}$$

where $f(Z) = \dfrac{1}{1 - 3Z^4 + Z^5}$. Equation (5) is written as

$$Z^6 - 3Z^5 + Z - 1000 = 0$$

which has the only real root $\overline{Z} \approx 3.988$. And thus Y, X values are obtaind as $\overline{Y} = (0.1)Z \approx 0.3988$, $\overline{X} = (0.01)Z \approx 0.03988$.

The linearized system of (3) around the unique positive constant steady-state $(\overline{X}, \overline{Y}, \overline{Z})$ is written with new variables

$$\tilde{X}(t) = X(t) - \overline{X}, \quad \tilde{Y}(t) = Y(t) - \overline{Y}, \quad \tilde{Z}(t) = Z(t) - \overline{Z}$$

as follows :

$$\begin{pmatrix} \dfrac{d\tilde{X}}{dt} \\ \dfrac{d\tilde{Y}}{dt} \\ \dfrac{d\tilde{Z}}{dt} \end{pmatrix} = A \begin{pmatrix} \tilde{X} \\ \tilde{Y} \\ \tilde{Z} \end{pmatrix}, \tag{6}$$

where A is the Jacobian matrix of system (3) at the steady-state $(\overline{X},\overline{Y},\overline{Z})$, that is

$$A = \begin{pmatrix} -0.1 & 0 & f'(\overline{Z}) \\ 1 & -0.1 & 0 \\ 0 & 1 & -0.1 \end{pmatrix}$$

where $f(Z) = \dfrac{1}{1-3Z^4+Z^5}$, and thus

$$f'(Z) = \frac{12Z^3-5Z^4}{(1-3Z^4+Z^5)^2} = (f(Z))^2\, Z^3(12-5Z).$$

Now from the relationship (5) we have that

$$f'(\overline{Z}) = (0.1)^6\, \overline{Z}^5(12-5\overline{Z}) \approx -0.00800522.$$

Now the characteristic equation of the Jacobian A is

$$(\lambda+0.1)^3 - f'(\overline{Z}) = 0$$

and thus we have eigenvalues of A:

$$\begin{aligned} \lambda_1 &\approx -0.300044 \\ \lambda_2 &\approx 2.17616\times 10^{-5} - 0.173243\, i \\ \lambda_3 &\approx 2.17616\times 10^{-5} + 0.173243\, i. \end{aligned}$$

Here the largest real part of the eigenvalues is positive. Thus the unique positive constant steady-state $(\overline{X},\overline{Y},\overline{Z})$ is unstable. □

Theorem 2. *In Case 2 the system* (4) *possesses a unique positive constant steady-state* $\left(\overline{X},\overline{Y},\overline{Z}\right) \approx (0.03107, 0.3107, 3.107)$ *which is stable.*

Proof. To find steady-states of the system (4) similarily as in Theorem 1 we obtain the equation

$$Z^7 - 2Z^6 + Z - 1000 = 0$$

which has the only root $\overline{Z} \approx 3.107$. And thus Y, X values are obtaind as $\overline{Y} = (0.1)\,Z \approx 0.3107$, $\overline{X} = (0.01)\,Z \approx 0.03107$.

Similarly as in Theorem 1 the Jacobian matrix A for the linearized system of (4) around the unique positive constant steady-state $(\overline{X}, \overline{Y}, \overline{Z})$ is

$$A = \begin{pmatrix} -0.1 & 0 & f'(\overline{Z}) \\ 1 & -0.1 & 0 \\ 0 & 1 & -0.1 \end{pmatrix}$$

where $f(Z) = \dfrac{1}{1-2Z^5+Z^6}$, and thus

$$f'(Z) = \frac{10Z^4 - 6Z^5}{(1-2Z^5+Z^6)^2} = (f(Z))^2\, Z^4 (10-6Z).$$

Now using the similar relationship as (5) in Theorem 1 we have that

$$f'(\overline{Z}) = (0.1)^6\, \overline{Z}^6 (10 - 6\overline{Z}) \approx -0.00778183.$$

Now the characteristic equation of the Jacobian A is

$$(\lambda + 0.1)^3 - f'(\overline{Z}) = 0$$

and thus we have eigenvalues of A:

$$\begin{aligned} \lambda_1 &\approx -0.298165 \\ \lambda_2 &\approx -9.17443 \times 10^{-4} - 0.171616\,i \\ \lambda_3 &\approx -9.17443 \times 10^{-4} + 0.171616\,i. \end{aligned}$$

Here all the real part of the eigenvalues are negative. Thus the unique positive constant steady-state $(\overline{X}, \overline{Y}, \overline{Z})$ is stable. □

3. Limit Cycles of the Modified Goodwin Model

Now we consider the two examples in Case 1 and 2 for the modified Goodwin model (2) to examine limit cycle phenomenon around the unique positive steady-state.

In Case 1 the functional response of the system (3) satiesfies that

$$\frac{1}{1-3Z^4+Z^5} > 0 \quad \text{for } Z > Z^* \approx 2.98745,$$

$$\frac{1}{1-3Z^4+Z^5} = \frac{1}{1+Z^4(Z-3)} \leq 1 \quad \text{for } Z \geq 3.$$

The numerical simulation in Figure 1 shows that the solution $X(t)$, $Y(t)$, $Z(t)$ of system (3) with the initial condition $X(0) = 0.01$, $Y(0) = 0.1$, $Z(0) = 5$. Here we observe that $Z(t) \geq 3$ for all $t \geq 0$ so the condition $0 < \frac{1}{1-3Z^4+Z^5} < 1$ in Lemma 1 holds to ensure the positiveness and boundedness of the soultion. In particular, in this case the system (3) exhibits limit cycle oscillation around the unique positive steady-state $(\overline{X}, \overline{Y}, \overline{Z}) \approx (0.03988, 0.3988, 3.988)$.

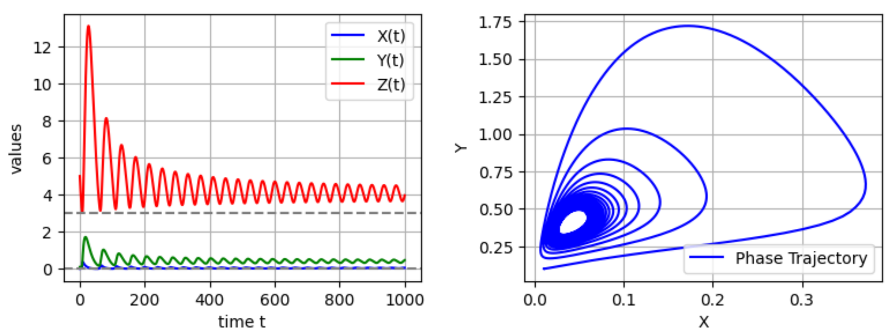

FIGURE 1. Left: Plots of $X(t)$, $Y(t)$, $Z(t)$, Right: Phase portrait of $(X(t), Y(t))$ for Case 1 : $n = 5$ with $X(0) = 0.01$, $Y(0) = 0.1$, $Z(0) = 5$

In Case 2 the functional response of the system (4) satiesfies that

$$\frac{1}{1-2Z^5+Z^6} > 0 \quad \text{for } Z > Z^* \approx 1.96595.$$

$$\frac{1}{1-2Z^5+Z^6} = \frac{1}{1+Z^5(Z-2)} \leq 1 \quad \text{for } Z \geq 2.$$

The numerical simulation in Figure 2 shows that the solution $X(t)$, $Y(t)$, $Z(t)$ of system (4) with the initial condition $X(0) = 0.01$, $Y(0) = 0.1$, $Z(0) = 4$. Here we observe that $Z(t) \geq 2$ for all $t \geq 0$ so the condition $0 < \frac{1}{1-2Z^5+Z^6} < 1$ in Lemma 1 holds to ensure the positiveness and boundedness of the soultion. In particular, in this case the system (4) exhibits limit cycle oscillation around the unique positive steady-state $\left(\overline{X},\overline{Y},\overline{Z}\right) \approx (0.03107, 0.3107, 3.107)$.

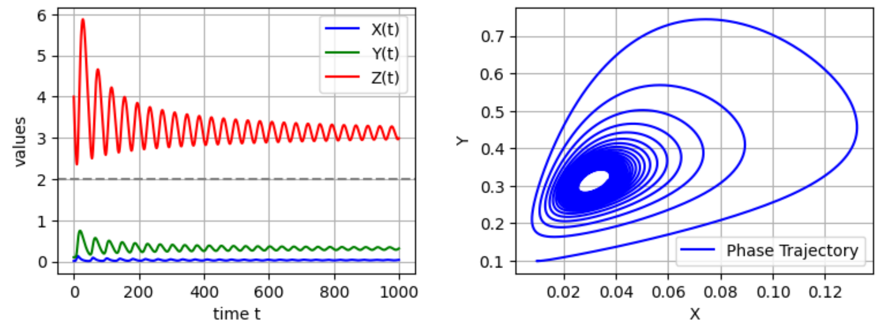

FIGURE 2. Left: Plots of $X(t)$, $Y(t)$, $Z(t)$, Right: Phase portrait of $(X(t),Y(t))$ for Case 2 : $n=6$ with $X(0)=0.01$, $Y(0)=0.1$, $Z(0)=4$

Figure 3 compares the graphs of functional responses of the modified Goodwin models (3) and (4) with the original Goodwin model (1). We can see that the functional response $\frac{K^n}{K^n-aZ+Z^n}$ is larger than the functional response $\frac{K^n}{K^n+Z^n}$ for a modest range of Z, even though they have almost same value for large Z.

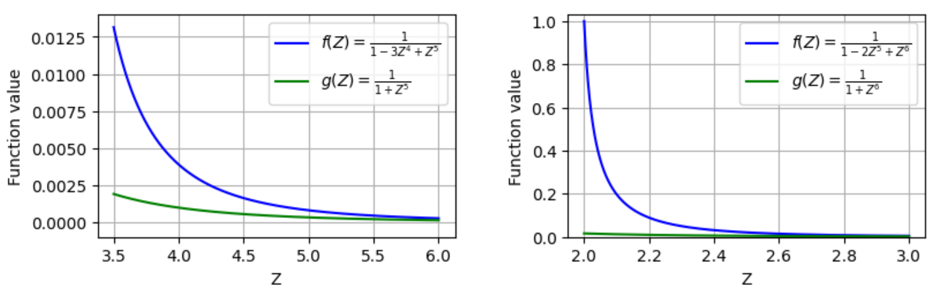

FIGURE 3. Comparison plots of functional responses in Case 1 (left) and Case 2 (right) with corresponding Goodwin models

Compared with the modified Goodwin models (3) and (4), the original Goodwin model (1) does not exhibit oscillatory behavior for functional order $n \leq 8$. In Figure 4 and 5 numerical simutions show damping solutions for the original Goodwin model (1) with the same parameters and initial conditions as in Figure 1 and 2, respectively.

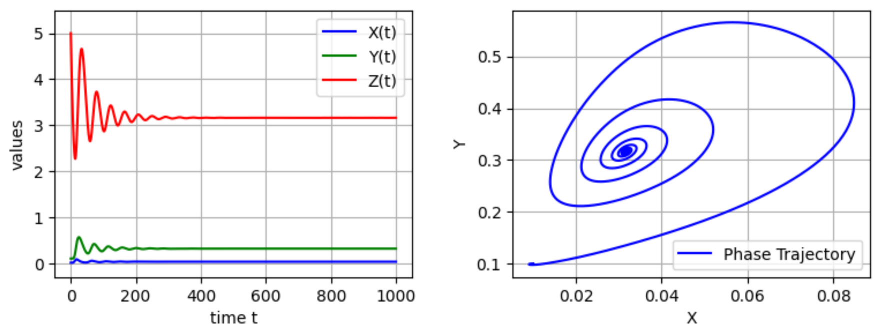

FIGURE 4. Left: Plots of $X(t)$, $Y(t)$, $Z(t)$, Right: Phase portrait of $(X(t), Y(t))$ for Goodwin Model (1) with $n = 5$, $k_1 = k_3 = k_5 = 1$, $k_2 = k_4 = k_6 = 0.1$, $K = 1$, and $X(0) = 0.01$, $Y(0) = 0.1$, $Z(0) = 5$

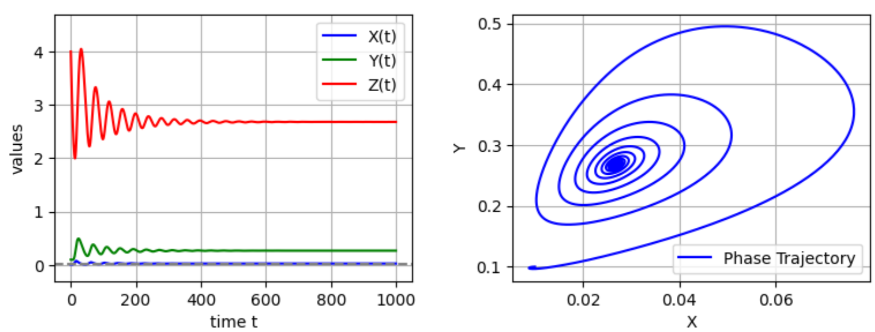

FIGURE 5. Left: Plots of $X(t)$, $Y(t)$, $Z(t)$, Right: Phase portrait of $(X(t), Y(t))$ for Goodwin Model (1) with $n = 6$ $k_1 = k_3 = k_5 = 1$, $k_2 = k_4 = k_6 = 0.1$, $K = 1$, and $X(0) = 0.01$, $Y(0) = 0.1$, $Z(0) = 4$

As shown in studies such as [5, 7], the Goodwin model (1) exhibits oscillatory behavior for functional orders $n > 8$. In Figure 6 numerical simutions show a limit cycle oscillation for the original Goodwin model (1) with $n = 10$ and all other parameters and initial conditions same as in Case 2.

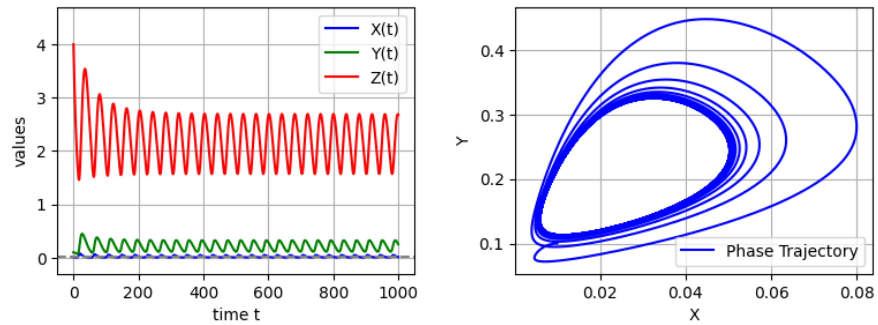

FIGURE 6. Left: Plots of $X(t)$, $Y(t)$, $Z(t)$, Right: Phase portrait of $(X(t), Y(t))$ for Goodwin Model (1) with $n = 10$, $k_1 = k_3 = k_5 = 1$, $k_2 = k_4 = k_6 = 0.1$, $K = 1$, and $X(0) = 0.01$, $Y(0) = 0.1$, $Z(0) = 4$

4. CONCLUSIONS

In this study, we propose some modified types of functional responses of the Goodwin model to construct models that demonstrate oscillatory behaviors. Constructing and analyzing mathematical models that can reproduce various oscillation phenomena is an important topic in biology and chemistry. The original Goodwind model is the prototype model of a negative feedback loop that exhibits oscillations. But it has been criticized for exhibiting oscillations when the cooperativity is very high, $n > 8$, which is unrealistic in most biological situations.

In this paper we examined two cases of a modified Goodwin model which exhibit periodic oscillations with functional responses of order $n = 5$ and $n = 6$. These results suggest the various possibilities of constructing models to have oscillatory solutions with lower order functional responses than the requirement $n > 8$ for the original Goodwin model case.

In Case 1 the system (3) possesses a unique positive constant steady-state $\left(\overline{X}, \overline{Y}, \overline{Z}\right)$ which is unstable. Thus the Poincaré-Bendixson theorem assures the existence of a limit cycle in the invariant region $\Omega = \{(X,Y,Z) \mid X > 0, Y > 0, Z > 0\}$ and a numerical simulation shows it as in Figre 1. In Case 2 the system (4) possesses a unique positive constant steady-state $\left(\overline{X}, \overline{Y}, \overline{Z}\right)$ which is stable and a numerical simulation shows a limit cycle as in Figre 2. In this case the Poincaré-Bendixson theorem does not apply and further mathematical investigations are needed to prove the existence of a limit cycle soultion. For example, Hopf bifurcation analysis can be a way to investigate oscillatory solutions, as in the paper [16] dealing with genetic negative feedback loops.

We have shown that in the modified model (3) the functional response $\frac{K^n}{K^n - aZ^{n-1} + Z^n}$ leads to produce oscillatory solutions when the order of the functional response is $n = 5$ or $n = 6$. In further studies, we will investigate the mathematical mechanisms underlying the differences between the modified model and the original Goodwin model.

Conflict of Interests

The author declares that there is no conflict of interests.

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