Periodic oscillation of the solutions for a Parkinson's disease model

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Abstract: In this paper, the oscillation of the solutions for a Parkinson's disease model with multiple delays is discussed. By linearizing the system at the equilibrium point and analyzing the instability of the linearized system, some sufficient conditions to guarantee the existence of periodic oscillation of the solutions for a delayed Parkinson's disease system are obtained. It is found that under suitable conditions on the parameters, time delay affects the stability of the system. The present method does not need to consider a bifurcating equation. Some numerical simulations are provided to illustrate our theoretical prediction.

Keywords: delayed Parkinson's disease model, instability, periodic solution

AMS Mathematical Subject Classification: 34K13

Original Research Article

1 Introduction

It is known that the beta oscillations in the basal ganglia may be induced by anomalous interaction of circuits that consist of the subthalamic nucleus (STN) and the globus pallidus pars externa (GPe). The STN and the GPe form an inhibitory-excitatory coupling loop. Holgado et al. provided the following oscillation model [1]:

$$\begin{cases} \tau_S S'(t) = F_S(-W_{GS}G(t-T_{GS}) + W_{TS}Ctx) - S(t), \\ \tau_G G'(t) = F_G(-W_{SG}S(t-T_{SG}) - W_{GG}G(t-T_{GG}) - W_{XG}Str) - G(t), \end{cases} \tag{1}$$

where $S(t)$ and $G\ (t)$ represent the average discharge rates of STN and GPe, respectively; $S(t-T)$, $G(t-T)$ represent the corresponding delay discharge rates. F_S and F_G are the activation functions of population S and G, showing the effect of synaptic input on the average discharge rate. W_{AB} are the weights of the connections from neural population A to neural population B. T_{AB} is the transmission delay of connections from population A to population B. The authors identified a simple set of necessary conditions on model parameters that guarantee the existence of beta oscillations in the model (1). Many authors have investigated the nonlinear dynamics in Parkinson's disease by means of the experimental method or analysis method [2-27]. For example, Wang et al. described the model by mean-field firing rate equations with discrete and distributed delays [12]:

$$\begin{cases} \tau_S S'(t) = F_S(-W_{GS}G(t-T_{GS}) + W_{CS}\int_{-\infty}^{t} K_1(t-s)E(s)ds) - S(t), \\ \tau_G G'(t) = F_G(W_{SG}S(t-T_{SG}) - W_{GG}\int_{-\infty}^{t} K_2(t-s)G(s)ds - Str) - G(t), \\ \tau_E E'(t) = F_E(-W_{SC}\int_{-\infty}^{t} K_3(t-s)S(s)ds - INN + c) - E(t), \end{cases} \tag{2}$$

where $E(t)$ represents the firing rate of cortical excitatory pyramidal neurons (EXN). The authors studied the absolutely stable, conditional stable, conditional oscillation, and absolutely oscillation for model (2), which can explain different mechanisms of oscillation origin. Wang et al. systematically studied Parkinson's oscillation origin mechanism, oscillation amplitude and frequency characteristics in an improved cortex-basal ganglia (EXN-INN-STN-GPe) resonance model as follows [14]:

$$\begin{cases} \tau_S S'(t) = F_S(-W_{GS}G(t-T_{GS}) + W_{CS}E(t-T_{CS})) - S(t), \\ \tau_G G'(t) = F_G(W_{SG}S(t-T_{SG}) - Str) - G(t), \\ \tau_E E'(t) = F_E(-W_{CC}I(t-T_{CC}) - W_{SC}S(t-T_{SC}) + C) - E(t), \\ \tau_I I'(t) = F_I(W_{CC}E(t-T_{CC})) - I(t), \end{cases} \tag{3}$$

where $F_Y(x) = \frac{M_Y}{1+((M_Y-B_Y)/B_Y)exp(-4x/M_Y)}(Y = S, G, E, I)$ are activation functions, $I(t)$ represents the firing rate of inhibitory nuclei (INN). Assume that $\tau_S = \tau_G = \tau_E = \tau_I = 15, T_{SG} = T_{GS} = T_{CS} = T_{CC} = T_{EE} = T$, the Hopf bifurcation of system (3) was considered. For a modified model of the system (3) as follows:

$$\begin{cases} \tau_S S'(t) = F_S(-W_{GS}G(t-T_{GS}) + W_{CS}E(t-T_{CS})) - S(t), \\ \tau_G G'(t) = F_G(W_{SG}S(t-T_{SG}) - Str) - G(t), \\ \tau_E E'(t) = F_E(-W_{CC}I(t-T_{CC}) + W_{EE}E(t-T_{EE}) + C) - E(t), \\ \tau_I I'(t) = F_I(W_{CC}E(t-T_{CC}) - W_{II}I(t-T_{II})) - I(t). \end{cases} \tag{4}$$

Assume that

$$\tau_S = \tau_G = \tau_E = \tau_I = 10, T_{SG} = T_{GS} = T_1, T_{CS} = T_{CC} = T_{EE} = T_{II} = T_2 \tag{5}$$

The Hopf bifurcation critical condition of the system (4) was provided. However, no matter what $\tau = 15, T_{SG} = T_{GS} = T_{CS} = T_{CC} = T_{SC} = T$, or condition (5), those always are special cases for the parameter values. According to the simulation result in [16], the parameters $\tau_S = 12.80ms, \tau_G = 20ms, \tau_E =$ 10–$20ms$, and $\tau_I =$ 10–$20ms$. Therefore, the results in [14] and [16] are only for special parameters. In this paper we study the dynamic behavior for model (4) under general parameter values and do not use the bifurcation method. For convenience, we rewrite model (4) as the following:

$$\begin{cases} S'(t) = -r_1 S(t) + r_1 F_S(-W_{GS}G(t-T_{GS}) + W_{CS}E(t-T_{CS})), \\ G'(t) = -r_2 G(t) + r_2 F_G(W_{SG}S(t-T_{SG}) - Str), \\ E'(t) = -r_3 E(t) + r_3 F_E(-W_{CC}I(t-T_{CC}) + W_{EE}E(t-T_{EE}) + C), \\ I'(t) = -r_4 I(t) + r_4 F_I(W_{CC}E(t-T_{CC}) - W_{II}I(t-T_{II})), \end{cases} \tag{6}$$

where $r_1 = \frac{1}{\tau_S}, r_2 = \frac{1}{\tau_G}, r_3 = \frac{1}{\tau_E}, r_4 = \frac{1}{\tau_I}$. From $F_Y(x) = \frac{M_Y}{1+((M_Y-B_Y)/B_Y)exp(-4x/M_Y)}$ we know that $F_S < M_S, F_G < M_G, F_E < M_E$, and $F_I < M_I$. Therefore,

$$\begin{cases} S'(t) < -r_1 S(t) + \tau_1 M_S, \\ G'(t) < -r_2 G(t) + \tau_2 M_G, \\ E'(t) < -r_3 E(t) + \tau_3 M_E, \\ I'(t) < -r_4 I(t) + \tau_4 M_I. \end{cases} \tag{7}$$

System (7) implies that $|S(t)| < \frac{r_1 M_S}{r_1} = M_S, |G(t)| < \frac{r_2 M_G}{r_2} = M_G, |E(t)| < \frac{r_3 M_E}{r_3} = M_E$, and $|I(t)| < \frac{r_4 M_I}{r_4} = M_I$, in other words, all of the solutions of system (4) are boundedness. According to the parameter values in [16]: M_S=300 spk/s, B_S=17 spk/s, M_G=400 spk/s, B_G=75 spk/s, M_E=71.77 spk/s, B_E=3.62 spk/s, M_I=276 spk/s, B_I=7.18 spk/s, we know that $F_Y(x)$ are monoton increasing functions for $Y = S, G, E$, and I. Therefore system (4) has a unique equilibrium point $(S^*, G^*.E^*, I^*)^T$. Make the change of variables $S(t) \to S(t) - S^*, G(t) \to G(t) - G^*, E(t) \to E(t) - E^*, I(t) \to I(t) - I^*$, the Taylor expansion of system (4) at the equilibrium point is the following:

$$\begin{cases} S'(t) = -r_1 S(t) + a_{12}G(t-T_{GS}) + a_{13}E(t-T_{CS}) \\ \qquad + \sum_{i+j\geq 2} \frac{[G(t-T_{GS})]^i}{i!} \frac{[E(t-T_{CS})]^j}{j!} \cdot \frac{\partial^{i+j} F_S}{\partial G^i \partial E^j}|_{(G^*,E^*)}, \\ G'(t) = -r_2 G(t) + a_{21}S(t-T_{SG}) + F''_G|_{S^*} S^2(t-T_{SG}) + \cdots, \\ E'(t) = -r_3 E(t) + a_{33}E(t-T_{EE}) + a_{34}I(t-T_{CC}) \\ \qquad + \sum_{i+j\geq 2} \frac{[E(t-T_{EE})]^i}{i!} \frac{[I(t-T_{CC})]^j}{j!} \cdot \frac{\partial^{i+j} F_E}{\partial E^i \partial I^j}|_{(E^*,I^*)}, \\ I'(t) = -r_4 I(t) + a_{43}E(t-T_{CC}) + a_{44}I(t-T_{II}) \\ \qquad + \sum_{i+j\geq 2} \frac{[E(t-T_{CC})]^i}{i!} \frac{[I(t-T_{II})]^j}{j!} \cdot \frac{\partial^{i+j} F_I}{\partial E^i \partial I^j}|_{(E^*,I^*)}, \end{cases} \tag{8}$$

where $a_{12}=r_1\frac{\partial F_S}{\partial G}|_{(G^*,E^*)}, a_{13}=r_1\frac{\partial F_S}{\partial E}|_{(G^*,E^*)}, a_{21}=r_2F'_G|_{S^*}, a_{33}=r_3\frac{\partial F_E}{\partial E}|_{(E^*,I^*)}, a_{34}=r_3\frac{\partial F_E}{\partial I}|_{(E^*,I^*)}, a_{43}=r_4\frac{\partial F_I}{\partial E}|_{(E^*,I^*)}, a_{44}=r_4\frac{\partial F_I}{\partial I}|_{(E^*,I^*)}$. The linearized system of system (8) is the follows:

$$\begin{cases} S'(t)=-r_1S(t)+a_{12}G(t-T_{GS})+a_{13}E(t-T_{CS}),\\ G'(t)=-r_2G(t)+a_{21}S(t-T_{SG}),\\ E'(t)=-r_3E(t)+a_{33}E(t-T_{EE})+a_{34}I(t-T_{CC}),\\ I'(t)=-r_4I(t)+a_{43}E(t-T_{CC})+a_{44}I(t-T_{II}), \end{cases} \tag{9}$$

Let $s=\min\{T_{GS},T_{CS},T_{SG},T_{EE},T_{CC},T_{II}\}$. Consider a special case of the system (9):

$$\begin{cases} S'(t)=-r_1S(t)+a_{12}G(t-s)+a_{13}E(t-s),\\ G'(t)=-r_2G(t)+a_{21}S(t-s),\\ E'(t)=-r_3E(t)+a_{33}E(t-s)+a_{34}I(t-s),\\ I'(t)=-r_4I(t)+a_{43}E(t-s)+a_{44}I(t-s), \end{cases} \tag{10}$$

The matrix form of the system (10) is as follows:

$$u'(t)=Cu(t)+Au(t-s), \tag{11}$$

where $u(t)=[S(t),G(t),E(t),I(t)]^T, u(t-s)=[S(t-s),G(t-s),E(t-s),I(t-s)]^T$, and

$$A=(a_{ij})_{4\times4}=\begin{pmatrix} 0 & a_{12} & a_{13} & 0\\ a_{21} & 0 & 0 & 0\\ 0 & 0 & a_{33} & a_{34}\\ 0 & 0 & a_{43} & a_{44} \end{pmatrix},$$

$$B=(b_{ij})_{4\times4}=diag(-r_1-r_2-r_3-r_4).$$

2 The existence of periodic solution

Since the system (9) is a linearized system of (8). Thus, we can see that the system (8) is a disturbed system of (9). If the trivial solution of system (9) is unstable, then the trivial solution of system (8) is also unstable. In what follows, we first consider the instability of the zero equilibrium point of the system (10) (or (11)). So we have the following Theorems.

Theorem 1. Assume that the system (11) has a unique trivial solution, $\alpha_1,\alpha_2,\alpha_3,\alpha_4$ are characteristic values of matrix A. If there is a characteristic value, say α_1,

(i) $Re(\alpha_1)=0, Im(\alpha_1)\neq 0$, and $\alpha_1=\omega i$;

(ii) $Re(\alpha_1) > 0$, and $Re(\alpha_1) > \max\{r_1, \cdots, r_4\}$,

(iii) $Im(\alpha_1) = 0, \alpha_1 > 0$ and $\alpha_1 > \max\{r_1, \cdots, r_4\}$. Then the trivial solution of system (11) (thus the system (8)) is unstable, implying that there exists a limit cycle in the system (4), namely, system (4) has a periodic solution.

Proof. We will show that the trivial solution of the system (11) is unstable. When $Re(\alpha_1) = 0, Im(\alpha_1) \neq 0$, and $\alpha_1 = \omega i$, then $e^{\omega i t} = \cos\omega t + i \sin\omega t$. Since $\cos\omega t$ is a periodic function, therefore, the trivial solution of system (11) is unstable. Obviously, all characteristic values of matrix B are $-r_1, -r_2, -r_3, -r_4$. Since $\alpha_1, \alpha_2, \alpha_3, \alpha_4$ are characteristic values of matrix A, then the characteristic equation of the system (11) is the following:

$$\Pi_{i=1}^{4} \lambda + r_i - \alpha_i e^{-\lambda s} = 0. \tag{12}$$

So we have

$$\lambda + r_1 - \alpha_1 e^{-\lambda s} = 0. \tag{13}$$

If $Re(\alpha_1) > 0$, and $Re(\alpha_1) > \max\{r_1, \cdots, r_4\}$, or $\alpha_1 > 0$, and $\alpha_1 > \max\{r_1, \cdots, r_4\}$, this means that the equation (13) has a positive real part characteristic value or a positive characteristic value. It suggests that the trivial solution of the system (11) is unstable. According to the basic theory of delayed differential equation, if the trivial solution is unstable for a small delay, then the trivial solution is still unstable as the delay increases [28]. In other words, the trivial solution of system (9) is unstable. This implies that the equilibrium point $(S^*, G^*.E^*, I^*)^T$ of system (8) is unstable. Equivalently, the unique equilibrium point of the system (4) is unstable. This instability of the unique equilibrium point together with the boundedness of the solutions will force system (4) to generate a limit cycle, namely, a periodic solution according to the extended Chafee's criterion [29, 30].The proof is completed.

Let $m = \max\{|a_{21}|, |a_{12}|, a_{33} + |a_{13}| + |a_{43}|, a_{44} + |a_{34}|, \}$ then we have

Theorem 2. Assume that the system (11) has a unique trivial solution. If the following condition holds

$$m - \tau > 0. \tag{14}$$

where $\tau = \min\{r_1, \cdots, r_4\}$. Then the trivial solution of system (11) is unstable, implying that there exists a limit cycle of system (4), namely, system (4) has a periodic solution.

Proof. To prove the instability of the trivial solution of the system (11), Let $z(t) =$

$|S(t)|+|G(t)|+|E(t)|+|I(t)|$. Therefore, $z(t)>0$ for $t>0$, and

$$z'(t) \leq -\tau z(t) + mz(t-s). \tag{15}$$

Specifically, consider a scalar equation

$$v'(t) = -\tau z(t) + mz(t-s). \tag{16}$$

According to the comparison theory of differential equation, we have $z(t) \leq v(t)$. We claim that the trivial solution of equation (16) is unstable. Indeed, the characteristic equation of (16) is as follows:

$$\lambda = -\tau + me^{-\lambda s}. \tag{17}$$

Consider a function $\varphi(\lambda) = \lambda + \tau - me^{-\lambda s}$. Then $\varphi(\lambda)$ is a continuous function of λ. Noting that $\varphi(0) = \tau - m = -(m-\tau) < 0$. Obviously, there exists a $L>0$ such that $\varphi(L) = L + \tau - me^{-Ls} > 0$. By the Intermediate Value Theorem, there exists a $\lambda_0 \in (0, L)$ such that $\varphi(\lambda_0) = 0$. In other words, there exists a positive characteristic root of the equation (16), which means that the trivial solution of equation (15) is unstable, implying that the trivial solution of system (11), thus (4) is unstable. Similar to Theorem 1, the system (4) has a periodic solution. The proof is completed.

3 Computer simulation result

In model (4), according to the parameters in [16], setting $M_S = 300, M_G = 400, M_E = 72, M_I = 276, W_{GS} = 3, W_{CS} = 6, W_{SG} = 2.5, W_{II} = 0.1, W_{EE} = 1, W_{CC} = 3, B_G = 75, B_S = 17, B_E = 3.6, B_I = 7, C = 277, Str = 40$, when we select the time delay $T_{SG} = 15.2, T_{GS} = 15.3, T_{CS} = T_{CC} = T_{EE} = 15.4, T_{II} = 15.5$, firstly, $\tau_S = 20, \tau_G = 10, \tau_E = 10, \tau_I = 12.5$, namely, $r_1 = 0.05, r_2 = 0.1, r_3 = 0.1, r_4 = 0.08$, then the unique positive equilibrium point $(S^*, G^*, E^*, I^*) = (61.2085, 167.5346, 60.7945, 72.0425)$. Thus, $a_{12} = r_1 \frac{\partial F_S}{\partial G}|_{(G^*,E^*)} = -0.0055, a_{13} = r_1 \frac{\partial F_S}{\partial E}|_{(G^*,E^*)} = 0.0112, a_{21} = r_2 F'_G|_{S^*} = 0.1213, a_{33} = r_3 \frac{\partial F_E}{\partial E}|_{(E^*,I^*)} = -0.0963, a_{34} = r_3 \frac{\partial F_E}{\partial I}|_{(E^*,I^*)} = 0.0328, a_{43} = r_4 \frac{\partial F_I}{\partial E}|_{(E^*,I^*)} = 0.2186, a_{44} = r_4 \frac{\partial F_I}{\partial I}|_{(E^*,I^*)} = -0.0076$. The characteristic values of matrix A_1 are $0.0436, -0.1475, 0.0258i$, $-0.0258i$. Since there exists a characteristic value $0.0258i$, and the conditions of Theorem 1 are satisfied. There exists a periodic oscillatory solution (see Fig.1). Then setting $\tau_S = 12.5, \tau_G = 20, \tau_E = 12.5, \tau_I = 16$, namely, $r_1 = 0.08, r_2 = 0.05, r_3 =$

$0.08, r_4 = 0.0625$, the other parameters are the same as figure 1, then $(S^*, G^*, E^*, I^*) = (64.3124, 164.6548, 62.4903, 75.8162)$. There exists a periodic oscillatory solution (see Fig.2). When we select $\tau_S = 10, \tau_G = 12.5, \tau_E = 8, \tau_I = 5$, namely, $r_1 = 0.1, r_2 = 0.08, r_3 = 0.125, r_4 = 0.2$, the other parameters are the same as figure 1, then $(S^*, G^*, E^*, I^*) = (51.9186, 142.0682, 54.1432, 64.9544)$. There exists a periodic oscillatory solution (see Fig.3). When we select the time delay $T_{SG} = 24.8, T_{GS} = 25.5, T_{CS} = T_{EE} = 26.4, T_{CC} = 24.2, T_{II} = 24.5$, $\tau_S = 20, \tau_G = 10, \tau_E = 10, \tau_I = 12.5$, namely, $r_1 = 0.05, r_2 = 0.1, r_3 = 0.1, r_4 = 0.08$, then the unique positive equilibrium point $(S^*, G^*, E^*, I^*) = (79.7544, 143.0359, 49.5957, 66.1679)$. Thus, $a_{12} = -0.0623, a_{13} = 0.1246, a_{21} = 0.2487, a_{33} = -0.0641, a_{34} = 0.0213, a_{43} = 0.1352, a_{44} = -0.0046$. The characteristic values of matrix A_2 are $0.0271, -0.0975, 0.1245i, -0.1245i$, and the conditions of Theorem 1 are satisfied. There exists a periodic oscillatory solution (see Fig.4). Then setting $\tau_S = 10, \tau_G = 5, \tau_E = 5, \tau_I = 10$, namely, $r_1 = 0.1, r_2 = 0.2, r_3 = 0.2, r_4 = 0.05$ the other parameters are the same as figure 4, then $(S^*, G^*, E^*, I^*) = (88.6328, 209.1742, 56.4323, 68.6519)$. There exists a periodic oscillatory solution (see Fig.5). When we select $\tau_S = 20, \tau_G = 10, \tau_E = 6.25, \tau_I = 10$, namely, $r_1 = 0.05, r_2 = 0.1, r_3 = 0.16, r_4 = 0.1$, the other parameters are the same as figure 4, then $(S^*, G^*, E^*, I^*) = (42.4116, 178.3734, 52.2841, 62.1911)$. There exists a periodic oscillatory solution (see Fig.6). From the figures, we see that time delays affect the oscillatory frequency.

4 Conclusion

The present paper discusses the oscillation of the solutions for a Parkinson's disease model with multiple delays by means of the extended Chafee's criterion. Two sufficient conditions are provided to guarantee the existence of periodic solutions. We change the nonlinear model to an equivalent system. The instability of the solution of the equivalent system implies the instability of the equilibrium point of the original system. Our criterion is only a sufficient condition.

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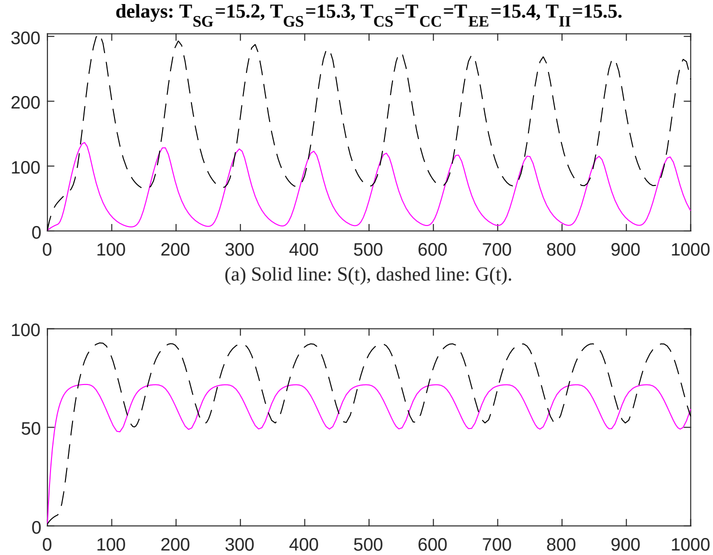
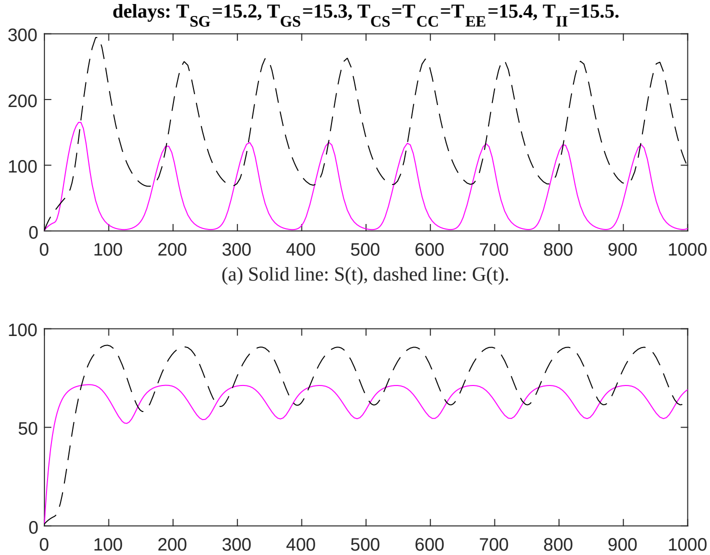
Fig.1 Periodic oscillation of the solutions, r_1=0.05, r_2=0.1, r_3=0.1, r_4=0.08, delays: T_{SG}=15.2, T_{GS}=15.3, T_{CS}=T_{CC}=T_{EE}=15.4, T_{II}=15.5.



(a) Solid line: S(t), dashed line: G(t).

(b) Solid line: E(t), dashed line: I(t).

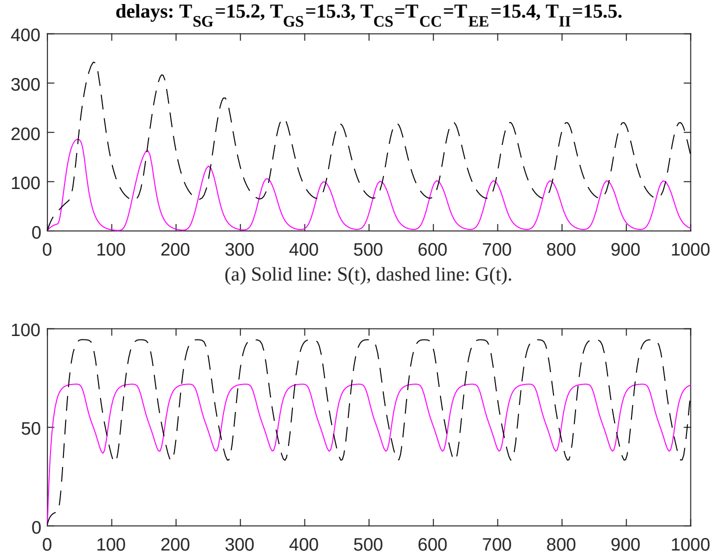
Fig.2 Periodic oscillation of the solutions, r_1=0.08, r_2=0.05, r_3=0.08, r_4=0.0625, delays: T_{SG}=15.2, T_{GS}=15.3, T_{CS}=T_{CC}=T_{EE}=15.4, T_{II}=15.5.



(a) Solid line: S(t), dashed line: G(t).

(b) Solid line: E(t), dashed line: I(t).

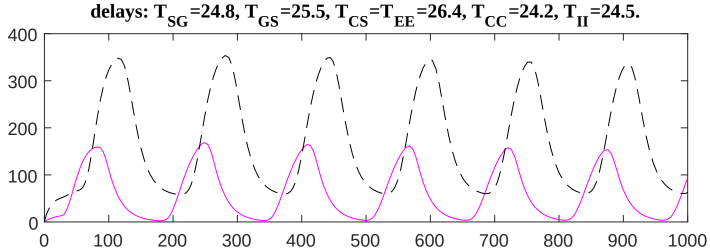
Fig.3 Periodic oscillation of the solutions, r_1=0.1, r_2=0.08, r_3=0.125, r_4=0.2, delays: T_{SG}=15.2, T_{GS}=15.3, T_{CS}=T_{CC}=T_{EE}=15.4, T_{II}=15.5.



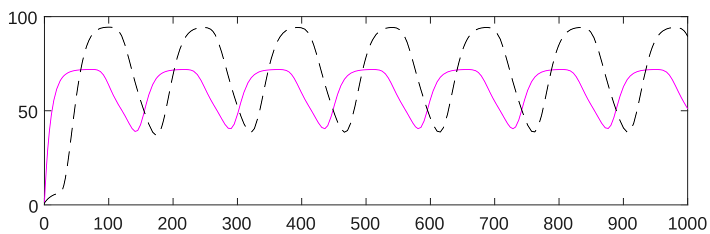
(a) Solid line: S(t), dashed line: G(t).

(b) Solid line: E(t), dashed line: I(t).

Fig.4 Periodic oscillation of the solutions, r_1=0.05, r_2=0.1, r_3=0.1, r_4=0.08,
delays: T_{SG}=24.8, T_{GS}=25.5, T_{CS}=T_{EE}=26.4, T_{CC}=24.2, T_{II}=24.5.

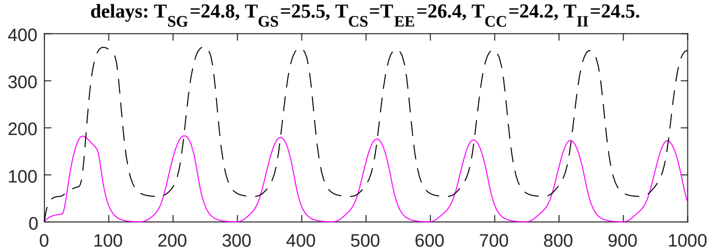


(a) Solid line: S(t), dashed line: G(t).

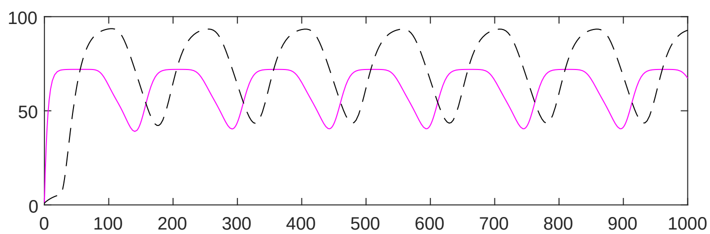


(b) Solid line: E(t), dashed line: I(t).

Fig.5 Periodic oscillation of the solutions, r_1=0.1, r_2=0.2, r_3=0.2, r_4=0.05, delays: T_{SG}=24.8, T_{GS}=25.5, T_{CS}=T_{EE}=26.4, T_{CC}=24.2, T_{II}=24.5.

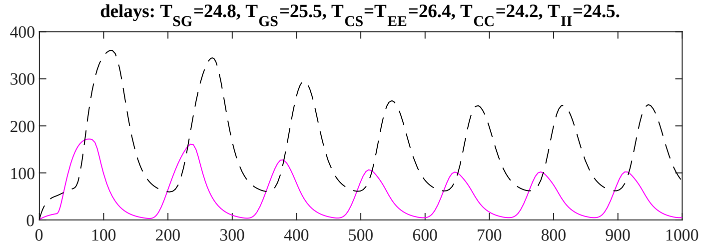


(a) Solid line: S(t), dashed line: G(t).

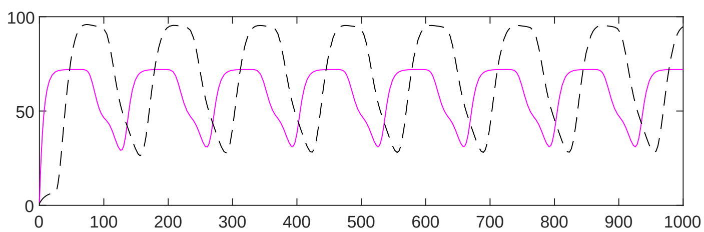


(b) Solid line: E(t), dashed line: I(t).

Fig.6 Periodic oscillation of the solutions, r_1=0.05, r_2=0.1, r_3=0.16, r_4=0.1, delays: T_{SG}=24.8, T_{GS}=25.5, T_{CS}=T_{EE}=26.4, T_{CC}=24.2, T_{II}=24.5.



(a) Solid line: S(t), dashed line: G(t).



(b) Solid line: E(t), dashed line: I(t).