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Stability and Hopf Bifurcation of a Target-Mediated Drug Disposition Model

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Abstract

In this paper, we study a three-dimensional target-mediated drug disposition model consisted of the drugs (ligands), targets (receptors) and drug-target (ligand-receptor) complexes. In this model, as the important drug administration method, a constant-rate intravenous continuous injection of the drugs is considered. Additionally, based on the nonlinear metabolism characteristics of drugs in human body, the drug reduction is described by the Michaelis-Menten equation. Firstly, the local stability of the positive equilibrium is investigated using the Routh-Hurwitz criterion. Then, by choosing the association rate of drugs and targets, which determines the effectiveness of drug binding to the target, as the bifurcation parameter, the existence conditions of Hopf bifurcation around the positive equilibrium are established. Finally, the stability of the bifurcating periodic solutions is also discussed by applying the Lyapunov index.

Keywords

TMDD Model, Stability, Hopf Bifurcation, Lyapunov Index

1. Introduction

Target-mediated drug disposition (TMDD) has been formally proposed to describe the high affinity phenomenon between drugs and biological targets [1]. The core connotation lies in that when a drug has an extremely high affinity for its target, the binding of the two is no longer an isolated event, but will significantly affect the distribution, metabolism and clearance pathways of the drug. Therefore, exploring this profound biomedical interaction between drugs and their targets has become extremely crucial for understanding the fate of drugs in the human body, predicting their efficacy, and even optimizing administration regimens. The dynamic mechanism of interaction between drugs and their targets is the core foundation for analyzing the processes of drug disposition. Traditional pharmacokinetic models often regard the disposal of drugs as a process relatively independent of their pharmacological effects. However, with the development of biopharmaceuticals, researchers have found that the high affinity binding of drugs to targets precisely constitutes the dominant factor driving their dynamic behavior *in vivo* [2] [3]. The TMDD model was induced and established under this cognitive leap. In the pharmacokinetics of biopharmaceuticals, the TMDD model has become a classic framework for describing the dynamic mechanism of drug-target interactions.

Mager and Jusko [4] systematically built the foundation of the TMDD model in 2001, a pharmacokinetic system defined by differential equations was proposed to quantitatively describe the drugs(ligands), targets(receptors), drug-target (ligand-receptor) complexes and the potential biological processes of them. In this basic turnover model for ligands binding to receptors, two-compartment ligands are assumed. Subsequently, the studies on characterizing TMDD by mathematical modeling have emerged continuously and received widespread attention. Gibiansky *et al.* [5] made outstanding contributions to the simplification and optimization of the TMDD model introduced in [4]. They conducted in-depth research on multiple forms such as Quasi-Equilibrium (QE) approximation, Quasi-Steady-State (QSS) approximation, and Michaelis-Menten (MM)approximation, and clarified the applicable conditions of different approximate models. Peletier *et al.* [6] focused on the interaction of ligand and receptor, omitted the second ligand compartment, and presented a one-compartment ligand TMDD model in which a ligand is supplied through an initial bolus or through a constant rate infusion. The evolution process of ligand, receptor and ligand-receptor complex concentrations was described through geometric methods, providing an intuitive approach for comparing the complete model with simplified models such as the QSS model, QE model and MM model in the one-compartment ligand situation. At the same time, the validity conditions of the parameters in TMDD model are also provided to ensure the applicability of these simplified models. Aston *et al.* [7] considered a TMDD model with mechanism-based reaction to explain the drug ligand-receptor interaction as follows:

$$\begin{cases} \dfrac{\mathrm{d}L}{\mathrm{d}t} = -k_{e(L)}L - k_{on}LR + k_{off}P, \\ \dfrac{\mathrm{d}R}{\mathrm{d}t} = k_{in} - k_{out}R - k_{on}LR + k_{off}P, \\ \dfrac{\mathrm{d}P}{\mathrm{d}t} = k_{on}LR - k_{off}P - k_{e(P)}P, \end{cases} \tag{1.1}$$

where L represents the drug ligand, R represents the receptor, and P represents the ligand-receptor complex. The rebound phenomenon in this model was investigated by using geometry and dynamical systems analysis. The possibility of free receptor levels rebounding to higher than the baseline level after one or more applications of an antibody drug was studied. From another perspective, Egbelowo *et al.* [8] studied the global dynamics of TMDD model mentioned above by nonstandard finite difference schemes. They firstly established positivity, boundedness, local and global asymptotic stability of the TMDD model. Secondly, positivity-preserving NSFD schemes are proposed and their dynamical properties are also analysed. In the study [9], Byun *et al.* derived the validity criteria of approximations of a two dimensional TMDD model to avoid over-parameterization and improve computational efficiency and analysis. They established the validity of three simplified TMDD models, and their results were confirmed with antibody-drug conjugate real-world data. The findings of this research provided a framework for selecting appropriate simplified TMDD models which can ensure the accuracy and yield accurate results. Just as described above, existing studies on the theoretical research that reveal the dynamic mechanism of the TMDD model remain scarce. Therefore, there is still considerable scope for further research.

In the classic TMDD model, the initial conditions usually simulate a single intravenous injection administration, that is, the drug enters the system by an initial concentration at the zero point in time. However, in clinical treatment and experimental research, constant-rate intravenous injection is a common and important method of drug administration. To precisely describe the pharmacokinetics under this administration scenario, we introduce an input constant of the drug into the model (1.1). Additionally, the drug presents a concentration-dependent nonlinear clearance in the body. Specifically, it is cleared rapidly at low concentrations, but the clearance rate slows down at high concentrations. Based on this nonlinear metabolic characteristic of the drug, we utilize the Michaelis-Menten equation to modify the linear drug clearance. Furthermore, the binding of drugs to their targets will simultaneously leads to a reduction in drugs, a decrease in targets, and an increase in drug-target complexes. Under normal circumstances, the drug reduction rate, the target decrease rate and the increase rate of drug-target complexes caused by such binding are generally regarded as different in a realistic way. Thus, we propose the following system of differential equations:

$$\begin{cases} \dfrac{\mathrm{d}M}{\mathrm{d}t} = \alpha + a_1 P - b_1 MT - \dfrac{V_m M^2}{k_m + M}, \\ \dfrac{\mathrm{d}T}{\mathrm{d}t} = \beta + a_2 P - b_2 MT - c_2 T, \\ \dfrac{\mathrm{d}P}{\mathrm{d}t} = b_3 MT - a_3 P - c_3 P, \end{cases} \tag{1.2}$$

where M, T, and P are the concentrations of the drug, target, and drug-target complex, respectively; α denotes the continuous intravenous injection rate; a_1 and b_1 represent the rates of drug increase (from drug-target complex dissociation) and decrease (due to binding of drug to target), respectively; V_m is the reaction rate when the target is saturated with the drug; k_m is the Michaelis constant; β is the drug turnover rate; a_2 and b_2 correspond to the target increase (from complex dissociation) and decrease (due to binding of drug to target) rates, respectively, while c_2 is the target elimination rate; Finally, for the drug-target complex, b_3 is the binding rate of the drugs to the targets, a_3 is the reduction rate (due to complex dissociation) and c_3 is elimination rate. Furthermore, based on practical considerations, we have $a_1 < a_3$, $a_2 < a_3$, $b_1 > b_3$ and $b_2 > b_3$. In fact, the drug-target complex is dissociated at rate a_3. Obviously, after the complex dissociates, only a portion of the drugs and targets will be released, rather than all of them. Therefore, the increase rates a_1 and a_2 of drug and target resulting from this will not exceed the dissociation rat a_3 of the complex. In addition, the drug and the target associate at rates b_1 and b_2 respectively. This combination will not completely generate the corresponding complex. Therefore, the increase rate of the resulting complex b_3 is less than b_1 and b_2.

2. Stability of Equilibrium and Existence of Hopf Bifurcation

This section is divided into two parts. We will discuss the stability of the positive equilibrium and the existence of Hopf bifurcation of system (1.2), respectively. Considering the biological meaning, we are interested in the existence of the positive equilibrium of system (1.2). For conveniens, we make the following assumptions:

(H_1) $\delta_1 = V_m\left[(a_3+c_3)b_2 - a_2b_3\right] > 0$;

(H_2) $\delta_2 = b_1(a_3+c_3)\beta - a_1b_3\beta - \alpha\left[(a_3+c_3)b_2 - a_2b_3\right] + V_m(a_3+c_3)c_2 < 0$.

Also, we denote

$$\delta_3 = b_1k_m\beta(a_3+c_3) - a_1b_3\beta k_m - \alpha\left[k_m(a_3+c_3)b_2 - k_ma_2b_3 + (a_3+c_3)c_2\right],$$

$$\delta_4 = -(a_3+c_3)c_2k_m\alpha.$$

Then, when (H_1)-(H_2) hold, we can obtain a unique positive equilibrium $E_* = (M_*, T_*, P_*)$ of system (1.2), where

$$P_* = \frac{b_2\beta M_*}{\left[(a_3+c_3)b_2 - a_2b_3\right]M_* + (a_3+c_3)c_2},$$

$$T_* = \frac{\beta(a_3+c_3)}{\left[(a_3+c_3)b_2 - a_2b_3\right]M_* + (a_3+c_3)c_2},$$

and M_* is the unique positive solution of cubic equation

$$\delta_1M^3 + \delta_2M^2 + \delta_3M + \delta_4 = 0. \tag{2.1}$$

In fact, let

$$p = \frac{3\delta_1\delta_3 - \delta_2^2}{3\delta_1^2},\quad q = \frac{2\delta_2^3 - 9\delta_1\delta_2\delta_3 + 27\delta_1^2\delta_4}{27\delta_1^3},\quad r = \frac{2\sqrt{3}}{9}\sqrt{|p|^3 + q^2}.$$

When (H_1)-(H_2) hold, we can see that $\delta_3 < 0$ and $\delta_4 < 0$. Then, this leads to $p < 0$, $q < 0$, and $r < 0$. Therefore, there exists a unique $M_* > 0$ satisfying cubic Equation (2.1), which means that system (1.2) has a unique positive equilibrium E_*.

Next, we linearize system (1.2) around E_* and obtain the corresponding Jacobian matrix

$$J=\begin{pmatrix} -b_1T_*-z & -b_1M_* & a_1 \\ -b_2T_* & -b_2M_*-c_2 & a_2 \\ -b_3T_* & b_3M_* & -a_3-c_3 \end{pmatrix},$$

in which $z=\dfrac{V_mM_*\left(2k_m+M_*\right)}{\left(k_m+M_*\right)^2}$. Obviously, we can get the characteristic equation of the linearized system of system (1.2) as follows:

$$\lambda^3+A\lambda^2+B\lambda+C=0, \tag{2.2}$$

where

$$\begin{aligned} A&=a_3+c_3+b_2M_*+c_2+b_1T_*+z,\\ B&=\left(a_3+c_3\right)\left(b_2M_*+c_2\right)-a_2b_3M_*\\ &\quad+\left(a_3+c_3+c_2\right)\left(b_1T_*+z\right)+b_2M_*z-a_1b_3T_*,\\ C&=\left(a_3+c_3\right)\left(b_2M_*z+b_1c_2T_*+c_2z\right)-a_2b_3M_*z-a_1b_3T_*c_2. \end{aligned}$$

Thus, we have the following theorem about the local stability of the positive equilibrium E_* of system (1.2).

Theorem 2.1. Suppose that (H$_1$)-(H$_2$) hold. If $\left(a_3+c_3+c_2\right)\left(b_1T_*+z\right)+b_2M_*z-a_1b_3T_*>0$ and $C>0$, then the positive equilibrium E_* of system (1.2) of system (1.2) is locally asymptotically stable.

Proof. It is obvious that $A>0$. If $\left(a_3+c_3+c_2\right)\left(b_1T_*+z\right)+b_2M_*z-a_1b_3T_*>0$ and $C>0$, then we see that $B>0$. Because of δ_1, we can calculate that

$$\begin{aligned} &AB-C\\ &=\left(a_3+c_3\right)\left[b_2M_*\left(a_3+c_3+b_2M_*+c_2+b_1T_*\right)+c_2\left(a_3+c_3+b_2M_*+c_2\right)\right]\\ &\quad-\left(a_3+c_3+b_2M_*+c_2+b_1T_*\right)a_2b_3M_*+\left(a_3+c_3+b_2M_*+c_2+b_1T_*+z\right)\\ &\quad\times\left[\left(a_3+c_3+c_2\right)\left(b_1T_*+z\right)+b_2M_*z-a_1b_3T_*\right]\\ &=M_*\left(b_2\left(a_3+c_3\right)-a_2b_3\right)\left(a_3+c_3+b_2M_*+c_2+b_1T_*\right)\\ &\quad+\left(a_3+c_3\right)c_2\left(a_3+c_3+b_2M_*+c_2\right)+\left(a_3+c_3+b_2M_*+c_2+b_1T_*+z\right)\\ &\quad\times\left[\left(a_3+c_3+c_2\right)\left(b_1T_*+z\right)+b_2M_*z-a_1b_3T_*\right]\\ &>0. \end{aligned}$$

Hence, the Routh-Hurwitz criterion is satisfied, all roots of the characteristic Equation (2.2) has negative real parts. Therefore, the positive equilibrium E_* is locally asymptotically stable. ☐

In the process of target-mediated drug disposition, parameter b_3 determines the effectiveness of the binding between the drug and the target, and significantly affects the dynamics of system (1.2). Therefore, when we study the bifurcation phenomenon of system (1.2), we choose b_3 as the bifurcation parameter reasonably. Denote $\Delta\overset{\text{def}}{=}AB-C$. In the situation that $\Delta=0$, it is obvious that the characteristic Equation (2.2) at E_* has one negative real root $\lambda_1=-A$, and a pair of purely imaginary roots $\lambda_2=i\omega$, $\lambda_3=-i\omega$ with $\omega=\sqrt{B}$. Let us define $\Delta\left(b_3\right)=A\left(b_3\right)B\left(b_3\right)-C\left(b_3\right)$. Without loss of generality, we suppose that there exists b_3^* such that

$$\Delta\left(b_3^*\right)=A\left(b_3^*\right)B\left(b_3^*\right)-C\left(b_3^*\right)=0. \tag{2.3}$$

Then, we present the following bifurcation result.

Theorem 2.2. Suppose that (H_1)-(H_2) hold. If there exists b_3^* such that $\Delta\left(b_3^*\right)=0$ and $C'\left(b_3^*\right)-A'\left(b_3^*\right)B\left(b_3^*\right)-A\left(b_3^*\right)B'\left(b_3^*\right)\neq 0$, then system (1.2) undergoes a Hopf bifurcation at E_*, where the symbol $'$ denotes the partial derivative with respect to b_3.

Proof. When $b_3=b_3^*$, it follows from (2.3) that $\Delta\left(b_3^*\right)=0$. The characteristic Equation (2.2) at E_* can be rewritten as follows:

$$\left(\lambda+A\left(b_3^*\right)\right)\left(\lambda^2+B\left(b_3^*\right)\right)=0. \tag{2.4}$$

Recall that $A>0$. It is clear that Equation (2.4) has three roots, namely: $\lambda_1=-A\left(b_3^*\right)$, $\lambda_2=i\omega$, $\lambda_3=-i\omega$ with $\omega=\sqrt{B\left(b_3^*\right)}$. When $0<\left|b_3-b_3^*\right|\ll 1$, differentiating the characteristic Equation (2.2) with respect to b_3 gives

$$3\lambda^2\lambda'+A'\lambda^2+2A\lambda\lambda'+B'\lambda+B\lambda'+C'=0,$$

where the symbol $'$ denotes the partial derivative with respect to b_3. Hence, we obtain

$$\lambda'\big|_{\lambda=\pm\omega i}=-\left.\frac{A'\lambda^2+B'\lambda+C'}{3\lambda^2+2A\lambda+B}\right|_{\lambda=\pm\omega i}=-\frac{C'-A'B\pm B'\sqrt{B}i}{-2B\pm 2A\sqrt{B}i}.$$

Therefore, if $C'\left(b_3^*\right)-A'\left(b_3^*\right)B\left(b_3^*\right)-A\left(b_3^*\right)B'\left(b_3^*\right)\neq 0$, then we have the transversality condition

$$\left.\left(\operatorname{Re}\left.\frac{\partial\lambda}{\partial b_3}\right|_{\lambda=\pm\omega i}\right)\right|_{b_3=b_3^*}=\frac{C'\left(b_3^*\right)-A'\left(b_3^*\right)B\left(b_3^*\right)-A\left(b_3^*\right)B'\left(b_3^*\right)}{2\left(B\left(b_3^*\right)+A^2\left(b_3^*\right)\right)}\neq 0.$$

Thus, system (1.2) satisfies the Hopf bifurcation theorem [10]-[12] undergoes a Hopf bifurcation around positive equilibrium E_*. ☐

3. Stability of Hopf Bifurcated Periodic Solution

In this section, we will determine the stability of Hopf bifurcated periodic solution of system (1.2) by using the Lyapunov stability index [13].

Theorem 3.1. Let L be defined by Equation (3.3). Suppose that the assumptions in Theorem 2.2 are satisfied. Then when b_3 undergoes a small perturbation around b_3^*, the following statements hold:

(i) If $L>0$, then an asymptotically stable periodic solution bifurcates from the Hopf bifurcation around the equilibrium E_*;

(ii) If $L<0$, then an unstable periodic solution bifurcates from the Hopf bifurcation around the equilibrium E_*.

Proof. The Jacobian matrix J at the equilibrium E_* when $b_3=b_3^*$ can be written as follows:

$$J=\begin{pmatrix}\alpha_{11} & \alpha_{12} & \alpha_{13}\\ \alpha_{21} & \alpha_{22} & \alpha_{23}\\ \alpha_{31} & \alpha_{32} & \alpha_{33}\end{pmatrix},$$

where

$$\begin{aligned}&\alpha_{11}=-b_1T_*-z,\quad \alpha_{12}=-b_1M_*,\quad \alpha_{13}=a_1,\\ &\alpha_{21}=-b_2T_*,\quad \alpha_{22}=-b_2M_*-c_2,\quad \alpha_{23}=a_2,\\ &\alpha_{31}=b_3^*T_*,\quad \alpha_{32}=-b_3^*M_*,\quad \alpha_{33}=-a_3-c_3.\end{aligned}$$

Note that $AB=C$, where A,B,C are defined by the expressions below the characteristic Equation (2.2). Then J has a negative eigenvalue $-A$ and a pair of purely imaginary eigenvalues $\pm i\omega$, where

$$\omega^2=\alpha_{22}\alpha_{33}-\alpha_{23}\alpha_{32}-c_2\alpha_{11}+\alpha_{11}\alpha_{33}-z\alpha_{22}-c_2z-\alpha_{13}\alpha_{31}.$$

Define the matrix

$$\overline{P}=\begin{pmatrix}c_{11} & c_{12} & c_{13}\\ c_{21} & c_{22} & c_{23}\\ c_{31} & c_{32} & c_{33}\end{pmatrix}.$$

All the elements of matrix P are defined as follows:

$$\begin{aligned}&c_{11}=\alpha_{11}\alpha_{13}+\alpha_{22}\alpha_{13}+\alpha_{13}\alpha_{33}-c_2\alpha_{13},\\ &c_{12}=-\frac{\left[\alpha_{33}\left(c_2\alpha_{11}+z\alpha_{22}+c_2z\right)+\omega^2\left(\alpha_{11}+\alpha_{22}+\alpha_{33}\right)\right]\left(\alpha_{11}+\alpha_{22}\right)}{\omega\alpha_{31}},\\ &c_{13}=-\alpha_{13}\left(c_2+\alpha_{33}\right),\\ &c_{21}=\alpha_{11}\alpha_{23}+\alpha_{22}\alpha_{33}+\alpha_{23}\alpha_{33}-z\alpha_{23},\\ &c_{22}=0,\\ &c_{23}=\frac{\alpha_{33}^2\left(\alpha_{11}+\alpha_{22}\right)-\alpha_{23}\alpha_{32}\left(\alpha_{33}+z\right)}{\alpha_{32}},\\ &c_{31}=-\left(\alpha_{11}+\alpha_{22}\right)\left(\alpha_{11}+\alpha_{22}+\alpha_{33}\right),\\ &c_{32}=\frac{\left(\alpha_{11}+\alpha_{22}\right)\left(c_2\alpha_{11}+z\alpha_{22}+c_2z\right)}{\omega},\\ &c_{33}=\alpha_{23}\alpha_{32}+c_2\alpha_{11}+z\alpha_{22}+\alpha_{13}\alpha_{31}-\alpha_{22}\alpha_{33}-\alpha_{11}\alpha_{33}.\end{aligned}$$

Through basic computations, the inverse matrix of $\overline{P}$ can be easily obtained from $\overline{P}$ as

$$\overline{P}^{-1}=\begin{pmatrix}d_{11} & d_{12} & d_{13}\\ d_{21} & d_{22} & d_{23}\\ d_{31} & d_{32} & d_{33}\end{pmatrix}=\frac{1}{\left|\overline{P}\right|}\begin{pmatrix}A_{11} & A_{21} & A_{31}\\ A_{12} & A_{22} & A_{32}\\ A_{13} & A_{23} & A_{33}\end{pmatrix},$$

where $\left|\overline{P}\right|$ is the determinant of $\overline{P}$, and A_{ij} is the corresponding algebraic cofactor $\left(1\le i,j\le 3\right)$,

$$\begin{aligned}A_{11}=&-\frac{1}{\omega\alpha_{32}}\left(\alpha_{11}+\alpha_{22}\right)\left(c_2\alpha_{11}+z\alpha_{22}+c_2z\right)\\ &\times\left[\alpha_{33}^2\left(\alpha_{11}+\alpha_{22}\right)-\alpha_{23}\alpha_{32}\left(\alpha_{33}+z\right)\right],\end{aligned}$$

$$\begin{aligned}
A_{12} = {} & \left[\alpha_{23}\left(\alpha_{11}+\alpha_{33}-z\right)+\alpha_{22}\alpha_{23}\right] \\
& \times\left(\alpha_{33}\left(\alpha_{22}+\alpha_{11}\right)-\alpha_{13}\alpha_{31}-z\left(c_2+\alpha_{22}\right)-c_2\alpha_{11}-\alpha_{23}\alpha_{32}\right) \\
& -\left(\alpha_{11}+\alpha_{22}\right)\left(\alpha_{11}+\alpha_{22}+\alpha_{33}\right)\alpha_{32}^{-1}\left[\alpha_{33}^2\left(\alpha_{11}+\alpha_{22}\right)-\alpha_{23}\alpha_{32}\left(\alpha_{33}+z\right)\right],
\end{aligned}$$

$$A_{13} = \frac{1}{\omega}\left(\alpha_{11}\alpha_{23}+\alpha_{22}\alpha_{33}+\alpha_{33}\alpha_{23}-z\alpha_{23}\right)\left(\alpha_{11}+\alpha_{22}\right)\left(c_2\alpha_{11}+z\alpha_{22}+c_2z\right),$$

$$\begin{aligned}
A_{21} = {} & \frac{1}{\omega\alpha_{31}}\left(\alpha_{11}+\alpha_{22}\right)\alpha_{33}\left(c_2\alpha_{11}+z\alpha_{22}+c_2z\right) \\
& \times\left(\alpha_{23}\alpha_{32}+c_2\alpha_{11}+z\alpha_{22}+c_2z+\alpha_{13}\alpha_{31}-\alpha_{22}\alpha_{33}-\alpha_{11}\alpha_{33}\right) \\
& +\omega\left(\alpha_{11}+\alpha_{22}+\alpha_{33}\right)\left(\alpha_{11}+\alpha_{22}\right)\alpha_{31}^{-1} \\
& \times\left(\alpha_{23}\alpha_{32}+c_2\alpha_{11}+z\alpha_{22}+c_2z+\alpha_{13}\alpha_{31}-\alpha_{22}\alpha_{33}-\alpha_{11}\alpha_{33}\right) \\
& -\omega^{-1}\alpha_{13}\left(c_2+\alpha_{33}\right)\left(\alpha_{11}+\alpha_{22}\right)\left(c_2\alpha_{11}+z\alpha_{22}+c_2z\right),
\end{aligned}$$

$$\begin{aligned}
A_{22} = {} & \alpha_{13}\left(\alpha_{11}+\alpha_{22}+\alpha_{33}-c_2\right) \\
& \times\left(\alpha_{23}\alpha_{32}+c_2\alpha_{11}+z\alpha_{22}+c_2z+\alpha_{13}\alpha_{31}-\alpha_{22}\alpha_{33}-\alpha_{11}\alpha_{33}\right) \\
& -\left(\alpha_{11}+\alpha_{22}\right)\alpha_{13}\left(c_2+\alpha_{33}\right)\left(\alpha_{11}+\alpha_{22}+\alpha_{33}\right),
\end{aligned}$$

$$\begin{aligned}
A_{23} = {} & \frac{1}{\alpha_{32}}\left[\alpha_{33}^2\left(\alpha_{11}+\alpha_{22}\right)-\alpha_{23}\alpha_{32}\left(\alpha_{33}+z\right)\right] \\
& \times\left(\alpha_{11}\alpha_{23}+\alpha_{22}\alpha_{33}+\alpha_{33}\alpha_{23}-z\alpha_{23}\right) \\
& -\left(\alpha_{11}\alpha_{13}+\alpha_{22}\alpha_{13}+\alpha_{33}\alpha_{13}-c_2\alpha_{13}\right) \\
& \times\left(\alpha_{22}\alpha_{33}+\alpha_{11}\alpha_{33}-\alpha_{13}\alpha_{31}-c_2z-\alpha_{22}z-c_2\alpha_{11}-\alpha_{23}\alpha_{32}\right),
\end{aligned}$$

$$A_{31} = \frac{1}{\omega}\left(\alpha_{11}\alpha_{23}+\alpha_{22}\alpha_{23}+\alpha_{33}\alpha_{23}-z\alpha_{23}\right)\left(\alpha_{11}+\alpha_{22}\right)\left(c_2\alpha_{11}+z\alpha_{22}+c_2z\right),$$

$$\begin{aligned}
A_{32} = {} & -\frac{1}{\omega}\left(\alpha_{11}\alpha_{13}+\alpha_{22}\alpha_{13}+\alpha_{33}\alpha_{13}-c_2\alpha_{13}\right)\left(\alpha_{11}+\alpha_{22}\right)\left(c_2\alpha_{11}+z\alpha_{22}+c_2z\right) \\
& -\frac{1}{\omega\alpha_{31}}\left(\alpha_{11}+\alpha_{22}\right)^2\left(\alpha_{11}+\alpha_{22}+\alpha_{33}\right) \\
& \times\left[\alpha_{33}\left(c_2\alpha_{11}+z\alpha_{22}+c_2z\right)+\omega^2\left(\alpha_{11}+\alpha_{22}+\alpha_{33}\right)\right],
\end{aligned}$$

$$\begin{aligned}
A_{33} = {} & -\frac{1}{\omega\alpha_{31}}\left(\alpha_{11}\alpha_{23}+\alpha_{22}\alpha_{33}+\alpha_{33}\alpha_{23}-z\alpha_{23}\right)\left(\alpha_{11}+\alpha_{22}\right) \\
& \times\left[\alpha_{33}\left(c_2\alpha_{11}+z\alpha_{22}+c_2z\right)+\omega^2\left(\alpha_{11}+\alpha_{22}+\alpha_{33}\right)\right].
\end{aligned}$$

Then, we can obtain the normal form

$$\bar{P}^{-1}J\bar{P} = \begin{pmatrix} 0 & \omega & 0 \\ -\omega & 0 & 0 \\ 0 & 0 & -A \end{pmatrix}.$$

We now determine the stability of the periodic solution bifurcating from the equilibrium E_*. First, we translate the equilibrium E_* to the origin by setting $M_1 = M - M_*$, $T_1 = T - T_*$, and $P_1 = P - P_*$. The Taylor expansion of the system (1.2) at the origin is then given by

$$\begin{pmatrix} \dfrac{\mathrm{d}M_1}{\mathrm{d}t} \\ \dfrac{\mathrm{d}T_1}{\mathrm{d}t} \\ \dfrac{\mathrm{d}P_1}{\mathrm{d}t} \end{pmatrix} = J\begin{pmatrix} M_1 \\ T_1 \\ P_1 \end{pmatrix} + \begin{pmatrix} h\left(M_1,T_1,P_1\right) \\ -b_2 M_1 T_1 \\ b_3 M_1 T \end{pmatrix}, \tag{3.1}$$

where

$$\begin{aligned} h\left(M_1,T_1,P_1\right) = & -\frac{V_m\left(k_m+M_*\right)^2-\left(2k_m+M_*\right)V_m M_*}{\left(k_m+M_*\right)^3}M_1^2-b_1 M_1 T_1 \\ & +\frac{3V_m\left(M_*^2+2k_m M_*+2k_m^2\right)-2V_m\left(k_m+M_*\right)^2}{6\left(k_m+M_*\right)^4}M_1^3 \\ & +Q_1\left(M_1,T_1,P_1\right), \end{aligned}$$

and $Q_1\left(M_1,T_1,P_1\right)$ is a C^∞-class power series of M_1, T_1 and P_1 with power higher than 3.

Next, we denote $X_1=\left(M_1,T_1,P_1\right)^{\mathrm{T}}$ and set $X_2=\bar{P}^{-1}X_1$, then system (3.1) is transformed into

$$\begin{aligned} \frac{\mathrm{d}X_2}{\mathrm{d}t} = \bar{P}^{-1}\frac{\mathrm{d}X_1}{\mathrm{d}t} & = \bar{P}^{-1}J\bar{P}X_2+\bar{P}^{-1}\begin{pmatrix} h\left(M_1,T_1,P_1\right) \\ -b_2 M_1 T_1 \\ b_3 M_1 T \end{pmatrix} \\ & \triangleq \begin{pmatrix} 0 & \omega & 0 \\ -\omega & 0 & 0 \\ 0 & 0 & -A \end{pmatrix} X_2+\bar{P}^{-1}\begin{pmatrix} H^1\left(M_2,T_2,P_2\right) \\ H^2\left(M_2,T_2,P_2\right) \\ H^3\left(M_2,T_2,P_2\right) \end{pmatrix}, \end{aligned} \tag{3.2}$$

in which

$$\begin{aligned} H^1\left(M_2,T_2,P_2\right) = & -\frac{V_m\left(k_m+M_*\right)^2-\left(2k_m+M_*\right)V_m M_*}{\left(k_m+M_*\right)^3} \\ & \times\left(c_{11}M_2+c_{12}T_2+c_{13}P_2\right)^2 \\ & -b_1\left(c_{11}M_2+c_{12}T_2+c_{13}P_2\right)\left(c_{21}M_2+c_{22}T_2+c_{23}P_2\right) \\ & +\frac{3V_m\left(M_*^2+2k_m M_*+2k_m^2\right)-2V_m\left(k_m+M_*\right)^2}{6\left(k_m+M_*\right)^4} \\ & \times\left(c_{11}M_2+c_{12}T_2+c_{13}P_2\right)^3, \end{aligned}$$

$$H^2\left(M_2,T_2,P_2\right)=-b_2\left(c_{11}M_2+c_{12}T_2+c_{13}P_2\right)\left(c_{21}M_2+c_{22}T_2+c_{23}P_2\right),$$

$$H^3\left(M_2,T_2,P_2\right)=b_3\left(c_{11}M_2+c_{12}T_2+c_{13}P_2\right)\left(c_{21}M_2+c_{22}T_2+c_{23}P_2\right).$$

Using system (0.8) to denote $F=\left(F^1,F^2,F^3\right)^{\mathrm{T}}=\bar{P}^{-1}\left(H^1,H^2,H^3\right)^{\mathrm{T}}$, we then obtain

$$F=\begin{pmatrix} F^1 \\ F^2 \\ F^3 \end{pmatrix}=\begin{pmatrix} d_{11}H^1+d_{12}H^2+d_{13}H^3 \\ d_{21}H^1+d_{22}H^2+d_{23}H^3 \\ d_{31}H^1+d_{32}H^2+d_{33}H^3 \end{pmatrix},$$

where d_{ij} is the element of matrix $\bar{P}^{-1}$ for $1 \le i, j \le 3$. The Lyapunov index L will be utilized to study the stability of the Hopf bifurcated periodic solution around the positive equilibrium E_*. To this end, we firstly need to determine the following terms in the Lyapunov index L:

$$\bar{F}_{11} = d_{31}H^1_{MM} + d_{32}H^2_{MM} + d_{33}H^3_{MM},\ \bar{F}_{12} = d_{31}H^1_{MT} + d_{32}H^2_{MT} + d_{33}H^3_{MT},$$

$$\bar{F}_{22} = d_{31}H^1_{TT} + d_{32}H^2_{TT} + d_{33}H^3_{TT},\ F^1_{11} = d_{11}H^1_{MM} + d_{12}H^2_{MM} + d_{13}H^3_{MM},$$

$$F^1_{22} = d_{11}H^1_{TT} + d_{12}H^2_{TT} + d_{13}H^3_{TT},\ F^1_{12} = d_{11}H^1_{MT} + d_{12}H^2_{MT} + d_{13}H^3_{MT},$$

$$F^2_{11} = d_{21}H^1_{MM} + d_{22}H^2_{MM} + d_{23}H^3_{MM},\ F^2_{22} = d_{21}H^1_{TT} + d_{22}H^2_{TT} + d_{23}H^3_{TT},$$

$$F^2_{12} = d_{21}H^1_{MT} + d_{22}H^2_{MT} + d_{23}H^3_{MT},\ F^1_{111} = d_{11}H^1_{MMM},$$

$$F^1_{122} = d_{11}H^1_{MTT},\ F^2_{112} = d_{21}H^1_{MMT},$$

$$F^2_{222} = d_{21}H^1_{TTT},\ G^1_2 = d_{11}H^1_{PT} + d_{12}H^2_{PT} + d_{13}H^3_{PT},$$

$$G^1_1 = d_{11}H^1_{MP} + d_{12}H^2_{MP} + d_{13}H^3_{MP},\ G^2_2 = d_{21}H^1_{PT} + d_{22}H^2_{PT} + d_{23}H^3_{PT},$$

in which

$$\begin{aligned} H^1_{MM} = {} & -c_{11}^2 \frac{2\left[V_m\left(k_m + M_*\right)^2 - \left(2k_m + M_*\right)V_m M_*\right]}{\left(k_m + M_*\right)^4} - 2b_1 c_{11} c_{21} \\ & + \frac{3V_m\left(M_*^2 + 2k_m M_* + 2k_m^2\right) - 2V_m\left(k_m + M_*\right)^2}{\left(k_m + M_*\right)^4} \\ & \times c_{11}^2\left(c_{11}M_2 + c_{12}T_2 + c_{13}P_2\right), \end{aligned}$$

$$\begin{aligned} H^1_{MT} = {} & -c_{11}c_{12} \frac{2\left[V_m\left(k_m + M_*\right)^2 - \left(2k_m + M_*\right)V_m M_*\right]}{\left(k_m + M_*\right)^4} - b_1\left(c_{11}c_{22} + c_{12}c_{21}\right) \\ & + \frac{3V_m\left(M_*^2 + 2k_m M_* + 2k_m^2\right) - 2V_m\left(k_m + M_*\right)^2}{\left(k_m + M_*\right)^4} \\ & \times c_{11}c_{12}\left(c_{11}M_2 + c_{12}T_2 + c_{13}P_2\right), \end{aligned}$$

$$\begin{aligned} H^1_{MP} = {} & -c_{11}c_{13} \frac{2\left[V_m\left(k_m + M_*\right)^2 - \left(2k_m + M_*\right)V_m M_*\right]}{\left(k_m + M_*\right)^4} - b_1\left(c_{11}c_{23} + c_{21}c_{13}\right) \\ & + \frac{3V_m\left(M_*^2 + 2k_m M_* + 2k_m^2\right) - 2V_m\left(k_m + M_*\right)^2}{\left(k_m + M_*\right)^4} \\ & \times c_{11}c_{13}\left(c_{11}M_2 + c_{12}T_2 + c_{13}P_2\right), \end{aligned}$$

$$\begin{aligned} H^1_{TT} = {} & -c_{12}^2 \frac{2\left[V_m\left(k_m + M_*\right)^2 - \left(2k_m + M_*\right)V_m M_*\right]}{\left(k_m + M_*\right)^4} - b_1\left(c_{12}c_{22} + c_{22}c_{12}\right) \\ & + \frac{3V_m\left(M_*^2 + 2k_m M_* + 2k_m^2\right) - 2V_m\left(k_m + M_*\right)^2}{\left(k_m + M_*\right)^4} \\ & \times c_{12}^2\left(c_{11}M_2 + c_{12}T_2 + c_{13}P_2\right), \end{aligned}$$

$$\begin{aligned}
H_{PT}^{1} &= -c_{12}c_{13}\frac{2\left[V_m\left(k_m+M_*\right)^2-\left(2k_m+M_*\right)V_mM_*\right]}{\left(k_m+M_*\right)^4}-b_1\left(c_{12}c_{23}+c_{22}c_{13}\right)\\
&\quad+\frac{3V_m\left(M_*^2+2k_mM_*+2k_m^2\right)-2V_m\left(k_m+M_*\right)^2}{\left(k_m+M_*\right)^4}\\
&\quad\times c_{12}c_{13}\left(c_{11}M_2+c_{12}T_2+c_{13}P_2\right),\\
H_{MMM}^{1} &= \frac{3V_m\left(M_*^2+2k_mM_*+2k_m^2\right)-2V_m\left(k_m+M_*\right)^2}{\left(k_m+M_*\right)^4}c_{11}^3\\
&\quad\times c_{12}c_{13}\left(c_{11}M_2+c_{12}T_2+c_{13}P_2\right),\\
H_{TTT}^{1} &= \frac{3V_m\left(M_*^2+2k_mM_*+2k_m^2\right)-2V_m\left(k_m+M_*\right)^2}{\left(k_m+M_*\right)^4}c_{12}^3,\\
H_{MTT}^{1} &= \frac{3V_m\left(M_*^2+2k_mM_*+2k_m^2\right)-2V_m\left(k_m+M_*\right)^2}{\left(k_m+M_*\right)^4}c_{12}^2c_{11},\\
H_{MMT}^{1} &= \frac{3V_m\left(M_*^2+2k_mM_*+2k_m^2\right)-2V_m\left(k_m+M_*\right)^2}{\left(k_m+M_*\right)^4}c_{12}c_{11}^2,\\
H_{MM}^{2} &= -2b_2c_{11}c_{21}, H_{MT}^{2}=-b_2\left(c_{11}c_{22}+c_{21}c_{12}\right),\\
H_{MMT}^{2} &= H_{MTT}^{2}=H_{MMM}^{2}=H_{TTT}^{2}=0,\\
H_{MP}^{2} &= -b_2\left(c_{11}c_{23}+c_{21}c_{13}\right), H_{TT}^{2}=-2b_2c_{11}c_{22},\\
H_{PT}^{2} &= -b_2\left(c_{11}c_{23}+c_{22}c_{13}\right),\\
H_{MM}^{3} &= 2b_3c_{11}c_{21}, H_{MT}^{3}=b_3\left(c_{11}c_{22}+c_{21}c_{12}\right),\\
H_{MMT}^{3} &= H_{MTT}^{3}=H_{MMM}^{3}=H_{TTT}^{3}=0,\\
H_{MP}^{3} &= b_3\left(c_{11}c_{23}+c_{21}c_{13}\right), H_{TT}^{3}=2b_3c_{11}c_{22},\\
H_{PT}^{3} &= b_3\left(c_{11}c_{23}+c_{22}c_{13}\right).
\end{aligned}$$

Thus, in conclusion, we can obtain the formula for the Lyapunov index L:

$$\begin{aligned}
L &= \frac{1}{\omega}\left[\left(F_{11}^1+F_{22}^1\right)F_{12}^1-\left(F_{11}^2+F_{22}^2\right)F_{12}^2-F_{11}^1F_{11}^2+F_{22}^1F_{22}^2\right]\\
&\quad-\left(F_{111}^1+F_{222}^1+F_{112}^1+F_{222}^2\right)\\
&\quad+\frac{1}{2\omega^2}\left(G_2^1+G_1^1\right)\left(1+\frac{A^2}{4\omega^2}\right)^{-1}\left[\omega\left(\bar{F}_{11}-\bar{F}_{22}\right)+A\bar{F}_{12}\right]\\
&\quad+\frac{2}{A}\left(G_2^2+G_1^1\right)\left(\bar{F}_{11}+\bar{F}_{22}\right)\\
&\quad-\frac{1}{4\omega^2}\left(G_2^2-G_1^1\right)\left(1+\frac{A^2}{4\omega^2}\right)^{-1}\left[A\left(\bar{F}_{11}-\bar{F}_{22}\right)-4\omega\bar{F}_{12}\right].
\end{aligned} \tag{3.3}$$

□

4. Conclusion

This paper investigates the dynamics of drug disposition model (1.2) with the interactions between drugs, targets and drug-target complexes. Firstly, the existence and local stability of the positive equilibrium are studied using the Hurwitz criterion. To study the Hopf bifurcation of model (1.2), we take the binding rate of the drug to the target b_3, which determines the effective binding of the drug to the corresponding target, as bifurcation parameter. Through the Hopf bifurcation theorem, the existence of Hopf bifurcation is analyzed. When certain sufficient conditions are satisfied, model (1.2) has a critical value b_3^* of b_3, which will makes the model (1.2) undergoes Hopf bifurcation at positive equilibrium when $b_3 = b_3^*$. Besides, when $b_3 > b_3^*$, the model (1.2) will bifurcate periodic solution, and the stability of the bifurcating periodic solution is discussed by constructing the Lyapunov index. From the obtained results, we see that when the binding rate b_3 of the drug to the target is smaller than a critical value b_3^*, drugs, targets and complexes will maintain a certain stable state under their mutual interaction. When the binding rate b_3 is larger than the critical value b_3^*, the model will exhibit periodic oscillation phenomenon. Based on the above findings, the following conclusions can be drawn regarding the drug-target binding rate: 1) When the binding rate remains below a specific threshold, model (1.2) can sustain its stability, thereby ensuring effective drug-target binding; 2) When the binding rate exceeds a certain level, model (1.2) can still be regulated to exhibit periodic oscillations within a bounded amplitude, allowing dynamic effective drug-target binding. Therefore, it is essential to maintain the drug-target binding rate within an appropriate and controlled range. In addition, there are relatively few theoretical analysis studies on the TMDD model. By introducing the constant drug injection and nonlinear metabolism, this study not only makes the TMDD model more in line with reality, but also enriches the theoretical research on the model dynamics. The boundary equilibrium point of simple TMDD model has been studied by previous literature, that is, the situation where both the drug and complex concentrations are zero and no binding of drug to target. This paper further explores the significant phenomenon that drug associates to its target to form complex after the drug injection, and conducts a theoretical study on the model dynamics under the interaction among the drug, target and their complex, which displayed that the binding between the drug and target determines the stable oscillations.

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Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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