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BIFURCATION OF NONTRIVIAL PERIODIC SOLUTIONS FOR PULSED CHEMOTHERAPY MODEL

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Abstract. A pulsed chemotherapeutic treatment model is investigated in this work. We prove the existence of nontrivial periodic solutions by the mean of Lyapunov-Schmidt bifurcation method of a cancer model. The results obtained are applied to the model with competition between normal, sensitive tumor and resistant tumor cells. The existence of bifurcated nontrivial periodic solutions are discussed with respect to the competition parameter values.

1. Introduction

A general impulsive mathematical model describing the dynamics of normal and tumor (sensitive and resistant) cells under the effect of impulsive chemotherapeutic treatment is studied in [4]. More specifically, the authors consider the following system

$$\dot{x_1} = \mathcal{F}_1(x_1, x_2, x_3), \tag{1.1}$$
$$\dot{x_2} = \mathcal{F}_2(x_1, x_2, x_3), \tag{1.2}$$
$$\dot{x_3} = \mathcal{F}_3(x_1, x_2, x_3), \tag{1.3}$$
$$x_1(t_i^+) = \Theta_1(x_1(t_i), x_2(t_i), x_3(t_i)), \tag{1.4}$$
$$x_2(t_i^+) = \Theta_2(x_1(t_i), x_2(t_i), x_3(t_i)), \tag{1.5}$$
$$x_3(t_i^+) = \Theta_3(x_1(t_i), x_2(t_i), x_3(t_i)), \tag{1.6}$$

where $t_{i+1} - t_i = cste = \tau > 0$, $\forall i \in \mathbb{N}$; $x_j \in \mathbb{R}$ and Θ_j are non-negative smooth functions, $\forall j = \overline{1,3}$,
τ: period between two successive drug treatment,
x_j: normal (resp. sensitive tumor and resistant tumor) cell biomass, for $j = 1$ (resp. 2,3),
$\Theta_j(x_1(t_i), x_2(t_i), x_3(t_i))$: fractions of normal (resp. sensitive tumor and resistant tumor) cells surviving the i^{th} drug treatment administered at time t_i for $j = 1$

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(resp. 2,3),
$\mathcal{F}_j(x_1, x_2, x_3)$: biomass growth of normal (resp. sensitive tumor and resistant tumor) cells for $j = 1$ (resp. 2,3).
The system (1.1)-(1.6) is studied in [4] , the authors prove the stability of trivial steady state solution and the existence of nontrivial periodic solution under the following assumptions

(A1): problem (1.1), (1.4), with $x_2 = x_3 = 0$ has a stable τ_0-periodic solution x_s,
(A2): the functions $\mathcal{F} = (\mathcal{F}_1, \mathcal{F}_2, \mathcal{F}_3)$ and $\Theta = (\Theta_1, \Theta_2, \Theta_3)$ are smooth enough,
(A3): $\mathcal{F}_2(x_1, 0, x_3) \equiv \Theta_2(x_1, 0, x_3) \equiv 0$, $\forall x_1,\ x_3 \in \mathbb{R}_+$,
(A4): $\mathcal{F}_3(x_1, 0, 0) \equiv \Theta_3(x_1, 0, 0) \equiv 0$, $\forall x_1 \in \mathbb{R}_+$,
(A5): $\Theta_i(x_1, x_2, x_3) \neq 0$ for $x_i \neq 0$, $i = 1, 2$,
(A6): $\Theta_3(x_1, x_2, x_3) \neq 0$ for $(x_2, x_3) \neq (0, 0)$, and
(A7): the positive octant is invariant with respect to the flow Φ associated to (1.1)-(1.3).

They reformulate the problem of finding nontrivial periodic solutions of (1.1)-(1.6) as a fixed point problem for the map

$$\begin{aligned} \Psi(\tau, .): \quad & \mathbb{R}^3_+ \to \mathbb{R}^3_+ \\ & X_0 \mapsto \Psi(\tau, X_0) = \Theta(\Phi(\tau, X_0)). \end{aligned}$$

That is

$$\Psi(\tau, X_0) = X_0. \tag{1.7}$$

Then $X(t) = \Phi(t, X_0)$ for $0 < t \leq \tau$ gives a τ-periodic solution of (1.1)-(1.6) if there exists $X_0 \in \mathbb{R}^3_+$ such that $X(\tau^+) = \Theta(X(\tau)) = \Theta(\Phi(\tau, X_0)) = \Psi(\tau, X_0) = X_0$.
From conditions **(Ai), i=1,. . .,7**, the problem (1.1)-(1.6) has a τ_0-periodic solution $\zeta(t) = (x_s(t), 0, 0)$ which is called a trivial solution.
To obtain the stability of the trivial fixed point $(x_s(0), 0, 0)$ associated to the trivial solution $(x_s, 0, 0)$ they determine the eigenvalues μ_j $(j = 1, 2, 3)$ of $D_X\Psi(\tau_0, X_0)$ where $\mu_j = \frac{\partial \Theta_j}{\partial x_j}(\Phi(\tau_0, X_0)) \exp\left(\int_0^{\tau_0} \frac{\partial \mathcal{F}_j}{\partial x_j}(\zeta(r))dr\right)$, and they obtain the following results.

Theorem 1.1. *(Theorem 1, [4]) If conditions* $\left|\dfrac{\partial \Theta_j}{\partial x_j}(\zeta(\tau_0))\right| \exp\left(\displaystyle\int_0^{\tau_0} \frac{\partial \mathcal{F}_j}{\partial x_j}(\zeta(r))dr\right)$ < 1 *for* $j = 1, 2, 3$ *are satisfied, then the trivial solution* $\zeta = (x_s, 0, 0)$ *is exponentially stable.*

They analyze the bifurcation of nontrivial solutions when the spectral radius $\rho(D_X\Psi(\tau_0, X_0)) = 1$ (see Iooss [2]). This case describes the lost of stability and the onset of the diseases expressed by the bifurcated solutions.
To this purpose, they use the following transformation $\tau = \tau_0 + \bar{\tau}$, $X = X_0 + \bar{X}$ and

$$N(\bar{\tau}, \bar{X}) = (N_1(\bar{\tau}, \bar{X}), N_2(\bar{\tau}, \bar{X}), N_3(\bar{\tau}, \bar{X})) = X_0 + \bar{X} - \Psi(\tau_0 + \bar{\tau}, X_0 + \bar{X}). \tag{1.8}$$

The fixed points of $\Psi(\tau_0 + \bar{\tau}, X_0 + \bar{X})$ are the solutions of

$$N(\bar{\tau}, \bar{X}) = 0. \tag{1.9}$$

To study the equation (1.9), the authors use the implicit function theorem and the Lyapunov-Schmidt bifurcation methods [1]. In fact $N(0,(0,0,0))=0$ and

$$E = D_X N(0,(0,0,0)) = \begin{pmatrix} a_0' & b_0' & c_0' \\ 0 & e_0' & 0 \\ 0 & h_0' & i_0' \end{pmatrix}$$

$$(1.10) \quad = \begin{pmatrix} 1-\frac{\partial\Theta_1}{\partial x_1}\frac{\partial\Phi_1}{\partial x_1} & -\sum_{i=1}^{3}\frac{\partial\Theta_1}{\partial x_i}\frac{\partial\Phi_i}{\partial x_2} & -\frac{\partial\Theta_1}{\partial x_1}\frac{\partial\Phi_1}{\partial x_3}-\frac{\partial\Theta_1}{\partial x_3}\frac{\partial\Phi_3}{\partial x_3} \\ 0 & 1-\frac{\partial\Theta_2}{\partial x_2}\frac{\partial\Phi_2}{\partial x_2} & 0 \\ 0 & -\sum_{i=2}^{3}\frac{\partial\Theta_3}{\partial x_i}\frac{\partial\Phi_i}{\partial x_2} & 1-\frac{\partial\Theta_3}{\partial x_3}\frac{\partial\Phi_3}{\partial x_3} \end{pmatrix}(\tau_0, X_0).$$

Critical cases correspond to $detE = a_0'e_0'i_0' = 0$, since $a_0' \neq 0$ (from (A1)), there are three cases **(C1)**: $e_0' = 0 \neq i_0'$, **(C2)**: $e_0' \neq 0 = i_0'$ and **(C3)**: $e_0' = i_0' = 0$ (see [4]). They obtain the following results.

Theorem 1.2. *(Theorem 2, case* **(C1)***, [4]) Let* $\left|\frac{\partial\Theta_j}{\partial x_j}(\zeta(\tau_0))\right| \exp\left(\int_0^{\tau_0}\frac{\partial\mathcal{F}_j}{\partial x_j}(\zeta(r))dr\right) < 1$ *for* $j=1,3$ *and* $\left|\frac{\partial\Theta_2}{\partial x_2}(\zeta(\tau_0))\right| \exp\left(\int_0^{\tau_0}\frac{\partial\mathcal{F}_2}{\partial x_2}(\zeta(r))dr\right) = 1$. *Then*
a) *for* $BC \neq 0$ *we have a bifurcation of nontrivial periodic solution of (1.1)-(1.6) with period* $\tau(\alpha) = \tau_0 + \bar\tau(\alpha)$ *starting from* $X_0 + \alpha Y_0 + Z^*(\bar\tau(\alpha),\alpha)$ *for* $\alpha > 0$ *small enough, moreover* $\bar\tau(\alpha) \simeq -\frac{C}{2B}\alpha$, *where* $Y_0 = \left(\frac{c_0'h_0'}{a_0'i_0'} - \frac{b_0'}{a_0'}, 1, -\frac{h_0'}{i_0'}\right)$, $Z^*(\bar\tau(\alpha),\alpha) = (z_1^*(\bar\tau(\alpha),\alpha), 0, z_3^*(\bar\tau(\alpha),\alpha))$ *and* $N_2(\bar\tau, \alpha Y_0 + Z^*(\bar\tau(\alpha),\alpha)) = B\bar\tau\alpha + C\frac{\alpha^2}{2} + o\left(|\alpha|^2 + |\bar\tau|^2\right)$,
b) *for* $BC = 0$ *we have an undetermined cases.*

Theorem 1.3. *(Theorem 3, case* **(C2)***, [4]) Let* $\left|\frac{\partial\Theta_j}{\partial x_j}(\zeta(\tau_0))\right| \exp\left(\int_0^{\tau_0}\frac{\partial\mathcal{F}_j}{\partial x_j}(\zeta(r))dr\right) < 1$ *for* $j=1,2$, $\left|\frac{\partial\Theta_3}{\partial x_3}(\zeta(\tau_0))\right| \exp\left(\int_0^{\tau_0}\frac{\partial\mathcal{F}_3}{\partial x_3}(\zeta(r))dr\right) = 1$ *and* $z_2^*(\bar\tau(\alpha),\alpha) \geq 0$ *(for* $\alpha > 0$ *small enough) be satisfied. Then*
a) *for* $BC \neq 0$ *we have a bifurcation of nontrivial periodic solutions of (1.1)-(1.6) with period* $\tau(\alpha) = \tau_0 + \bar\tau(\alpha)$ *starting from* $X_0 + \alpha Y_0 + Z^*(\bar\tau(\alpha),\alpha)$ *for* $\alpha > 0$ *small enough, moreover* $\bar\tau(\alpha) \simeq -\frac{C}{2B}\alpha$, *where* $Y_0 = \left(\frac{-c_0'}{a_0'}, 0, 1\right)$, $Z^*(\bar\tau(\alpha),\alpha) = (z_1^*(\bar\tau(\alpha),\alpha), z_2^*(\bar\tau(\alpha),\alpha), 0)$ *and* $N_3(\bar\tau, \alpha Y_0 + Z^*(\bar\tau(\alpha),\alpha)) = B\bar\tau\alpha + C\frac{\alpha^2}{2} + o\left(|\alpha|^2 + |\bar\tau|^2\right)$,

b) *for* $BC = 0$ *we have an undetermined cases.*

Remark 1.1. The function $Z^*(\bar\tau(\alpha),\alpha) = (z_1^*(\bar\tau(\alpha),\alpha), 0, z_3^*(\bar\tau(\alpha),\alpha))$ (resp. $Z^*(\bar\tau(\alpha),\alpha) = (z_1^*(\bar\tau(\alpha),\alpha), z_2^*(\bar\tau(\alpha),\alpha), 0)$) in theorem 1.2 (resp. theorem 1.3) is obtained by the mean of implicit function theorem for the system $(N_1, N_3)(\bar\tau, \alpha Y_0 + Z) = (0,0)$ (resp. $(N_1, N_2)(\bar\tau, \alpha Y_0 + Z) = (0,0)$).

The degenerate case **(C3)** corresponding to $e_0' = i_0' = 0$ is not studied in [4], it's investigated in this work and the results obtained are applied to the models studied by Lakmeche *et al.* [4] and Panetta [5]. Our paper is organized as follow, the next section contains our main results, applications of our results are given in section three, after that we give some concluding remarks. Computational details are contained in Appendixes.

2. Main result

In this section we analyze the bifurcation of nontrivial periodic solutions $\Phi(t, X_0)$ of period τ near ζ, which occur for $e'_0 = i'_0 = 0$. In our study, we investigate two cases corresponding to $h'_0 \neq 0$ and $h'_0 = 0$.

2.1. **For** $h'_0 \neq 0$**.** We have $\dim(\ker(E)) = 1$. Let $\ker(E) = span\{\mathcal{Y}_0\}$ where $\mathcal{Y}_0 = (\frac{-\acute{c}_0}{\acute{a}_0}, 0, 1)$, then the equation (1.9) is equivalent to

$$\left\{\begin{array}{l} N_1(\bar{\tau}, \alpha\mathcal{Y}_0 + \mathcal{Z}) = 0, \\ N_2(\bar{\tau}, \alpha\mathcal{Y}_0 + \mathcal{Z}) = 0, \\ N_3(\bar{\tau}, \alpha\mathcal{Y}_0 + \mathcal{Z}) = 0, \end{array}\right. \tag{2.1}$$

where $\mathcal{Z} = \mathsf{z}_1 e_1 + \mathsf{z}_2 e_2$, $e_1 = (1,0,0)$, $e_2 = (0,1,0)$, $(\alpha, \mathsf{z}_1, \mathsf{z}_2) \in \mathbb{R}^3$ and $\bar{X} = \alpha\mathcal{Y}_0 + \mathcal{Z}$. Since $\det D_{\mathcal{Z}}(N_1, N_3)(0,(0,0,0)) = \det \begin{pmatrix} a'_0 & b'_0 \\ 0 & h'_0 \end{pmatrix} = a'_0 h'_0 \neq 0$, there exist $\delta > 0$ sufficiently small and a unique continuous function $\mathcal{Z}^*$, such that $\mathcal{Z}^*(\bar{\tau}, \alpha) = (\mathsf{z}_1^*(\bar{\tau}, \alpha), \mathsf{z}_2^*(\bar{\tau}, \alpha), 0)$, $\mathcal{Z}^*(0,0) = (0,0,0)$,

$$N_1(\bar{\tau}, \alpha\mathcal{Y}_0 + \mathcal{Z}^*(\bar{\tau}, \alpha)) = 0 \tag{2.2}$$

and

$$N_3(\bar{\tau}, \alpha\mathcal{Y}_0 + \mathcal{Z}^*(\bar{\tau}, \alpha)) = 0, \tag{2.3}$$

for every $(\bar{\tau}, \alpha)$ such that $|\alpha| < \delta$ and $|\bar{\tau}| < \delta$.
Then $N(\bar{\tau}, \bar{X}) = 0$ if

$$\mathsf{f}_2(\bar{\tau}, \alpha) = N_2(\bar{\tau}, \alpha\mathcal{Y}_0 + \mathcal{Z}^*(\bar{\tau}, \alpha)) = 0. \tag{2.4}$$

Now, we proceed to solve equation (2.4). First, it's seen that $\mathsf{f}_2(0,0) = N_2(0,(0,0,0)) = 0$.
From the Taylor development of f_2 around $(\bar{\tau}, \alpha) = (0,0)$, we find that $\frac{\partial \mathsf{f}_2(0,0)}{\partial \bar{\tau}} = \frac{\partial \mathsf{f}_2(0,0)}{\partial \alpha} = 0$ and $\frac{\partial^2 \mathsf{f}_2(0,0)}{\partial \bar{\tau}^2} = \frac{\partial^2 \mathsf{f}_2(0,0)}{\partial \bar{\tau}\partial \alpha} = \frac{\partial^2 \mathsf{f}_2(0,0)}{\partial \alpha^2} = 0$ (see Appendix B, Subsections 5.2 and 5.3).
Furthermore, let $\mathcal{A}_2 = \frac{\partial^3 \mathsf{f}_2(0,0)}{\partial \bar{\tau}^3}$, $\mathcal{B}_2 = \frac{\partial^3 \mathsf{f}_2(0,0)}{\partial \bar{\tau}^2 \partial \alpha}$, $\mathcal{C}_2 = \frac{\partial^3 \mathsf{f}_2(0,0)}{\partial \alpha^3}$ and $\mathcal{D}_2 = \frac{\partial^3 \mathsf{f}_2(0,0)}{\partial \bar{\tau}\partial \alpha^2}$. It's shown that $\mathcal{A}_2 = 0$ (see Appendix B, Subsection 5.4). Hence,

$$\mathsf{f}_2(\bar{\tau}, \alpha) = \frac{\alpha}{6}(3\mathcal{B}_2\bar{\tau}^2 + 3\mathcal{D}_2\bar{\tau}\alpha + \mathcal{C}_2\alpha^2) + o_{(\bar{\tau},\alpha)}(|\alpha|^3 + |\bar{\tau}|^3).$$

Let $\rho \in \mathbb{R}$ such that $\bar{\tau} = \rho\alpha$, then $\mathsf{f}_2(\rho\alpha, \alpha) = \frac{\alpha^3}{6}\tilde{\mathsf{f}}_2(\rho, \alpha)$, with

$$\tilde{\mathsf{f}}_2(\rho, \alpha) = 3\mathcal{B}_2\rho^2 + 3\mathcal{D}_2\rho + \mathcal{C}_2 + o_\alpha(1 + |\rho|^3),$$

and

$$\tilde{\mathsf{f}}_2(\rho, 0) = 3\mathcal{B}_2\rho^2 + 3\mathcal{D}_2\rho + \mathcal{C}_2 = 0. \tag{2.5}$$

The equation $\tilde{\mathsf{f}}_2(\rho, \alpha) = 0$ is studied using implicit function theorem.
For $\mathcal{B}_2 = 0$, we have $\tilde{\mathsf{f}}_2(\rho, 0) = 3\mathcal{D}_2\rho + \mathcal{C}_2$ and $\frac{\partial \tilde{\mathsf{f}}_2}{\partial \rho}(\rho, 0) = 3\mathcal{D}_2$. So, for $\mathcal{D}_2 \neq 0$ and $\rho_0 = -\frac{\mathcal{C}_2}{2\mathcal{D}_2}$ we have $\tilde{\mathsf{f}}_2(\rho_0, 0) = 0$ and $\frac{\partial \tilde{\mathsf{f}}_2}{\partial \rho}(\rho_0, 0) \neq 0$, we find a function $\rho(\alpha)$ such that for α small enough $\tilde{\mathsf{f}}_2(\rho(\alpha), \alpha) = 0$ and $\rho(0) = \rho_0 = -\frac{\mathcal{C}_2}{2\mathcal{D}_2}$.
Then, for α near 0 and $\bar{\tau}(\alpha) = \rho(\alpha)\alpha$ we have $\mathsf{f}_2(\bar{\tau}(\alpha), \alpha) = 0$.

Theorem 2.1. *Let* $\left|\frac{\partial\Theta_1}{\partial x_1}(\zeta(\tau_0))\right| \exp\left(\int_0^{\tau_0} \frac{\partial\mathcal{F}_1(\zeta(r))}{\partial x_1} dr\right) < 1$, $\left|\frac{\partial\Theta_j}{\partial x_j}(\zeta(\tau_0))\right| \exp\left(\int_0^{\tau_0} \frac{\partial\mathcal{F}_j(\zeta(r))}{\partial x_j} dr\right) = 1$ *for* $j = 2, 3$, $h_0' \neq 0$ *and* $z_2^*(\bar{\tau}(\alpha), \alpha) \geq 0$ *for* $\alpha > 0$ *small enough. Then for* $\mathcal{C}_2\mathcal{D}_2 \neq 0 = \mathcal{B}_2$, *we have a bifurcation of one nontrivial* $\tau(\alpha)$*-periodic solution of* (1.1)-(1.6) *with initial condition* $\left(x_0 - \frac{c_0'}{a_0'}\alpha + z_1^*(\bar{\tau}(\alpha), \alpha), z_2^*(\bar{\tau}(\alpha), \alpha), \alpha\right)$ *and period* $\tau(\alpha) = \tau_0 + \bar{\tau}(\alpha)$ *for* $\alpha > 0$ *small enough, where* $\bar{\tau}(\alpha) = -\frac{\mathcal{C}_2}{3\mathcal{D}_2}\alpha + o(\alpha)$.

For $\mathcal{B}_2 \neq 0$, to solve equation $\tilde{\mathsf{f}}_2(\rho, 0) = 0$ we must calculate the discriminant Δ_ρ of equation (2.5), where $\Delta_\rho = 3(3\mathcal{D}_2^2 - 4\mathcal{B}_2\mathcal{C}_2)$. So, for $\Delta_\rho > 0$ (*i.e.* $\mathcal{B}_2\mathcal{C}_2 < \frac{3}{4}\mathcal{D}_2^2$) and $\mathcal{B}_2\mathcal{C}_2 \neq 0$ we have $\tilde{\mathsf{f}}_2(\rho_0^\pm, 0) = 0$ and $\frac{\partial\tilde{\mathsf{f}}_2}{\partial\rho}(\rho_0^\pm, 0) \neq 0$, where $\rho_0^\pm = \frac{-3\mathcal{D}_2 \pm \sqrt{9\mathcal{D}_2^2 - 12\mathcal{B}_2\mathcal{C}_2}}{6B_2}$, we find a function $\rho(\alpha)$ such that for α small enough $\tilde{\mathsf{f}}_2(\rho(\alpha), \alpha) = 0$ and $\rho(0) = \rho_0^\pm$. Then, for α near 0 and $\bar{\tau}(\alpha) = \rho(\alpha)\alpha$ we have $\mathsf{f}_2(\bar{\tau}(\alpha), \alpha) = 0$.
In conclusion we have the following theorem.

Theorem 2.2. *Let* $\left|\frac{\partial\Theta_1}{\partial x_1}(\zeta(\tau_0))\right| \exp\left(\int_0^{\tau_0} \frac{\partial\mathcal{F}_1(\zeta(r))}{\partial x_1} dr\right) < 1$, $\left|\frac{\partial\Theta_j}{\partial x_j}(\zeta(\tau_0))\right| \exp\left(\int_0^{\tau_0} \frac{\partial\mathcal{F}_j(\zeta(r))}{\partial x_j} dr\right) = 1$ *for* $j = 2, 3$ *and* $h_0' \neq 0$.
1) *If* $z_2^*(\bar{\tau}^\pm(\alpha), \alpha) \geq 0$ *for* $\alpha > 0$ *small enough and* $0 \neq \mathcal{B}_2\mathcal{C}_2 < \frac{3}{4}\mathcal{D}_2^2$, *then we have a bifurcation of two nontrivial* $(\tau_0 + \bar{\tau}^\pm(\alpha))$*-periodic solutions of* (1.1)-(1.6) *with initial conditions* $\left(x_0 - \frac{c_0'}{a_0'}\alpha + z_1^*(\bar{\tau}^\pm(\alpha), \alpha), z_2^*(\bar{\tau}^\pm(\alpha), \alpha), \alpha\right)$, *where* $\bar{\tau}^\pm(\alpha) = \frac{-3\mathcal{D}_2 \pm \sqrt{9\mathcal{D}_2^2 - 12\mathcal{B}_2\mathcal{C}_2}}{6\mathcal{B}_2}\alpha + o(\alpha)$.
2) *If* $z_2^*(\bar{\tau}^-(\alpha), \alpha) \geq 0$ *with* $z_2^*(\bar{\tau}^+(\alpha), \alpha) < 0$ *(resp.* $z_2^*(\bar{\tau}^-(\alpha), \alpha) < 0$ *with* $z_2^*(\bar{\tau}^+(\alpha), \alpha) \geq 0$*) for* $\alpha > 0$ *small enough and* $0 \neq \mathcal{B}_2\mathcal{C}_2 < \frac{3}{4}\mathcal{D}_2^2$, *then we have a bifurcation of one nontrivial* $(\tau_0 + \bar{\tau}^-(\alpha))$ *(resp.* $(\tau_0 + \bar{\tau}^+(\alpha))$*)-periodic solution of* (1.1)-(1.6) *with initial condition* $\left(x_0 - \frac{c_0'}{a_0'}\alpha + z_1^*(\bar{\tau}^-(\alpha), \alpha), z_2^*(\bar{\tau}^-(\alpha), \alpha), \alpha\right)$ *(resp.* $\left(x_0 - \frac{c_0'}{a_0'}\alpha + z_1^*(\bar{\tau}^+(\alpha), \alpha), z_2^*(\bar{\tau}^+(\alpha), \alpha), \alpha\right)$*), where* $\bar{\tau}^\pm(\alpha) = \frac{-3\mathcal{D}_2 \pm \sqrt{9\mathcal{D}_2^2 - 12\mathcal{B}_2\mathcal{C}_2}}{6\mathcal{B}_2}\alpha + o(\alpha)$.

2.2. **For** $h_0' = 0$**.** We have $\dim(\ker[E]) = 2$. Let $\ker(E) = span\{Y_0, Y_1\}$ where $Y_0 = (\frac{-\acute{b}_0}{\acute{a}_0}, 1, 0)$ and $Y_1 = (\frac{-\acute{c}_0}{\acute{a}_0}, 0, 1)$, then the equation $N(\bar{\tau}, \bar{X}) = 0$ is equivalent to

$$\begin{cases} N_1(\bar{\tau}, \alpha Y_0 + \beta Y_1 + Z) = 0, \\ N_2(\bar{\tau}, \alpha Y_0 + \beta Y_1 + Z) = 0, \\ N_3(\bar{\tau}, \alpha Y_0 + \beta Y_1 + Z) = 0, \end{cases} \tag{2.6}$$

where $Z = z_1 e_1$, $e_1 = (1, 0, 0)$ with $\alpha, \beta, z_1 \in \mathbb{R}$ and $\bar{X} = \alpha Y_0 + \beta Y_1 + Z$.
Since $\frac{\partial N_1}{\partial z_1}(0, (0, 0, 0)) = \frac{\partial N_1(0,(0,0,0))}{\partial x_1}\frac{\partial x_1}{\partial z_1} = \acute{a}_0 \neq 0$, there exist $\delta > 0$ small enough and a unique continuous function Z^*, such that $Z^*(\bar{\tau}, \alpha, \beta) = (z_1^*(\bar{\tau}, \alpha, \beta), 0, 0)$, $Z^*(0, 0, 0) = (0, 0, 0)$ and

$$N_1(\bar{\tau}, \alpha Y_0 + \beta Y_1 + Z^*(\bar{\tau}, \alpha, \beta)) = 0, \tag{2.7}$$

for $\max(|\bar{\tau}|, |\alpha|, |\beta|) < \delta$.
Then $N(\bar{\tau}, \bar{X}) = 0$ if

$$f_2(\bar{\tau}, \alpha, \beta) = N_2(\bar{\tau}, \alpha Y_0 + \beta Y_1 + Z^*(\bar{\tau}, \alpha, \beta)) = 0 \tag{2.8}$$

and

$$f_3(\bar{\tau},\alpha,\beta) = N_3(\bar{\tau},\alpha Y_0 + \beta Y_1 + Z^*(\bar{\tau},\alpha,\beta)) = 0. \tag{2.9}$$

Now, we proceed to solve (2.8) and (2.9). First, it is seen that $f_2(0,0,0) = N_2(0,(0,0,0)) = 0$ and $f_3(0,0,0) = N_3(0,(0,0,0)) = 0$.
From the Taylor development of f_2 and f_3 near $(\bar{\tau},\alpha,\beta) = (0,0,0)$, we find that $\frac{\partial f_2(0,0,0)}{\partial\bar{\tau}} = \frac{\partial f_3(0,0,0)}{\partial\bar{\tau}} = 0$, $\frac{\partial f_2(0,0,0)}{\partial\alpha} = \frac{\partial f_3(0,0,0)}{\partial\alpha} = 0$ and $\frac{\partial f_2(0,0,0)}{\partial\beta} = \frac{\partial f_3(0,0,0)}{\partial\beta} = 0$ (see Appendix C, Subsections 6.2 and 6.3).
Furthermore, let $A_j = \frac{\partial^2 f_j(0,0,0)}{\partial\bar{\tau}^2} = 0$, $B_j = \frac{\partial^2 f_j(0,0,0)}{\partial\alpha^2}$, $C_j = \frac{\partial^2 f_j(0,0,0)}{\partial\beta^2} = 0$, $D_j = \frac{\partial^2 f_j(0,0,0)}{\partial\bar{\tau}\partial\alpha}$, $E_j = \frac{\partial^2 f_j(0,0,0)}{\partial\bar{\tau}\partial\beta} = 0$ and $F_j = \frac{\partial^2 f_j(0,0,0)}{\partial\alpha\partial\beta}$ for $j = 2,3$.
It's shown that $A_2 = A_3 = 0$, $C_2 = 0$ and $E_2 = 0$.
Hence,

$$\begin{cases} f_2(\bar{\tau},\alpha,\beta) = & \frac{1}{2}\left(B_2\alpha^2 + 2D_2\bar{\tau}\alpha + 2F_2\alpha\beta\right) + o_{(\bar{\tau},\alpha,\beta)}(|\bar{\tau}|^2 + |\alpha|^2 + |\beta|^2), \\ \\ f_3(\bar{\tau},\alpha,\beta) = & \frac{1}{2}\left(B_3\alpha^2 + C_3\beta^2 + 2D_3\bar{\tau}\alpha + 2E_3\bar{\tau}\beta + 2F_3\alpha\beta\right) \\ & +o_{(\bar{\tau},\alpha,\beta)}(|\bar{\tau}|^2 + |\alpha|^2 + |\beta|^2). \end{cases}$$

Let $(\rho,\sigma) \in \mathbb{R}\times\mathbb{R}_+^*$ such that $\bar{\tau} = \rho\alpha$ and $\beta = \sigma\alpha$, then

$$\begin{cases} f_2(\rho\alpha,\alpha,\sigma\alpha) = \frac{\alpha^2}{2}\tilde{f}_2(\rho,\alpha,\sigma), \\ \\ f_3(\rho\alpha,\alpha,\sigma\alpha) = \frac{\alpha^2}{2}\tilde{f}_3(\rho,\alpha,\sigma), \end{cases}$$

where

$$\begin{cases} \tilde{f}_2(\rho,\alpha,\sigma) = B_2 + 2D_2\rho + 2F_2\sigma + o_\alpha(|\rho|^2 + 1 + |\sigma|^3), \\ \\ \tilde{f}_3(\rho,\alpha,\sigma) = B_3 + C_3\sigma^2 + 2D_3\rho + 2E_3\rho\sigma + 2F_3\sigma + o_\alpha(|\rho|^2 + 1 + |\sigma|^3). \end{cases}$$

We have

$$\begin{cases} \tilde{f}_2(\rho,0,\sigma) = B_2 + 2D_2\rho + 2F_2\sigma = 0, \\ \tilde{f}_3(\rho,0,\sigma) = B_3 + C_3\sigma^2 + 2D_3\rho + 2E_3\rho\sigma + 2F_3\sigma = 0, \end{cases} \tag{2.10}$$

and

$$\begin{aligned} J_{(\rho,\sigma)}(\tilde{f}_2,\tilde{f}_3)(\rho,0,\sigma) = &\ \det\begin{pmatrix} \frac{\partial\tilde{f}_2(\rho,0,\sigma)}{\partial\rho} & \frac{\partial\tilde{f}_2(\rho,0,\sigma)}{\partial\sigma} \\ \frac{\partial\tilde{f}_3(\rho,0,\sigma)}{\partial\rho} & \frac{\partial\tilde{f}_3(\rho,0,\sigma)}{\partial\sigma} \end{pmatrix} \\ = &\ 2\det\begin{pmatrix} D_2 & F_2 \\ D_3 + E_3\sigma & C_3\sigma + E_3\rho + F_3 \end{pmatrix}. \end{aligned}$$

To use the implicit function theorem, we have to find $(\rho_0,\sigma_0) \in \mathbb{R}\times\mathbb{R}_+^*$ such that $\tilde{f}_2(\rho_0,0,\sigma_0) = \tilde{f}_3(\rho_0,0,\sigma_0) = 0$ and $J_{(\rho,\sigma)}(\tilde{f}_2,\tilde{f}_3)(\rho_0,0,\sigma_0) \neq 0$.
In the following we give all the possible cases for bifurcation of nontrivial periodic solutions.
(H1) $F_2 = 0$, $D_2 \neq 0$, $C_3 = 0$, $\left(B_3 - \frac{D_3B_2}{D_2}\right)\left(2F_3 - \frac{E_3B_2}{D_2}\right) < 0$, $\rho_0 = \frac{-B_2}{2D_2}$ and $\sigma_0 = \left(-B_3 + \frac{D_3B_2}{D_2}\right)\left(2F_3 - \frac{E_3B_2}{D_2}\right)^{-1}$.
(H2) $F_2 = 0, D_2 \neq 0, C_3 > 0, B_3 - \frac{D_3B_2}{D_2} < 0, \rho_0 = \frac{-B_2}{2D_2}$ and $\sigma_0 = \frac{-\left(2F_3 - \frac{E_3B_2}{D_2}\right) + \sqrt{\left(2F_3 - \frac{E_3B_2}{D_2}\right)^2 - 4C_3\left(B_3 - \frac{D_3B_2}{D_2}\right)}}{2C_3}$.
(H3) $F_2 = 0$, $D_2 \neq 0$, $C_3 < 0$, $B_3 - \frac{D_3B_2}{D_2} > 0$, $\rho_0 = \frac{-B_2}{2D_2}$ and

$\sigma_0 = \dfrac{-\left(2F_3 - \frac{E_3B_2}{D_2}\right) - \sqrt{\left(2F_3 - \frac{E_3B_2}{D_2}\right)^2 - 4C_3\left(B_3 - \frac{D_3B_2}{D_2}\right)}}{2C_3}$.

(H4) $F_2 = 0$, $D_2 \neq 0$, $B_3 - \frac{D_3B_2}{D_2} = 0$, $\left(2F_3 - \frac{E_3B_2}{D_2}\right) C_3 < 0$, $\rho_0 = \frac{-B_2}{2D_2}$ and $\sigma_0 = \dfrac{-\left(2F_3 - \frac{E_3B_2}{D_2}\right)}{C_3}$.

(H5) $B_2F_2 < 0$, $D_2 = 0$, $2D_3 - \frac{E_3B_2}{F_2} \neq 0$, $\rho_0 = \dfrac{B_2\left(F_3 - \frac{C_3B_2}{4F_2}\right) - B_3F_2}{2F_2D_3 - E_3B_2}$ and $\sigma_0 = -\frac{B_2}{2F_2}$.

(H6) $F_2 \neq 0$, $\frac{C_3D_2}{F_2} - 2E_3 = 0$, $(D_2B_3 - B_2D_3)\left(D_3F_2 - D_2\left(F_3 - \frac{C_3B_2}{4F_2}\right)\right) > 0$,
$\rho_0 = \dfrac{B_2\left(F_3 - \frac{C_3B_2}{4F_2}\right) - B_3F_2}{2D_3F_2 - 2D_2\left(F_3 - \frac{C_3B_2}{4F_2}\right)}$ and $\sigma_0 = \dfrac{D_2B_3 - B_2D_3}{2D_3F_2 - 2D_2\left(F_3 - \frac{C_3B_2}{4F_2}\right)}$.

(H7) $F_2D_2 \neq 0$, $C_3\frac{D_2}{F_2} - 2E_3 < 0$, $D_2B_3 - B_2D_3 > 0$,

$$\rho_0 = -\frac{\frac{B_2}{F_2}\left(C_3\frac{D_2}{F_2} - 2E_3\right) + \frac{E_3B_2 - 2F_3D_2}{F_2} + 2D_3 - \sqrt{\left(\frac{E_3B_2 - 2F_3D_2}{F_2} + 2D_3\right)^2 - 4\frac{D_2B_3 - B_2D_3}{F_2}\left(C_3\frac{D_2}{F_2} - 2E_3\right)}}{2\frac{D_2}{F_2}\left(C_3\frac{D_2}{F_2} - 2E_3\right)}$$

and

$$\sigma_0 = \frac{\frac{E_3B_2 - 2F_3D_2}{F_2} + 2D_3 - \sqrt{\left(\frac{E_3B_2 - 2F_3D_2}{F_2} + 2D_3\right)^2 - 4\frac{D_2B_3 - B_2D_3}{F_2}\left(C_3\frac{D_2}{F_2} - 2E_3\right)}}{2\left(C_3\frac{D_2}{F_2} - 2E_3\right)}.$$

(H8) $F_2D_2 \neq 0$, $C_3\frac{D_2}{F_2} - 2E_3 > 0$, $D_2B_3 - B_2D_3 < 0$,

$$\rho_0 = -\frac{\frac{B_2}{F_2}\left(C_3\frac{D_2}{F_2} - 2E_3\right) + \frac{E_3B_2 - 2F_3D_2}{F_2} + 2D_3 + \sqrt{\left(\frac{E_3B_2 - 2F_3D_2}{F_2} + 2D_3\right)^2 - 4\frac{D_2B_3 - B_2D_3}{F_2}\left(C_3\frac{D_2}{F_2} - 2E_3\right)}}{2\frac{D_2}{F_2}\left(C_3\frac{D_2}{F_2} - 2E_3\right)}$$

and

$$\sigma_0 = \frac{\frac{E_3B_2 - 2F_3D_2}{F_2} + 2D_3 + \sqrt{\left(\frac{E_3B_2 - 2F_3D_2}{F_2} + 2D_3\right)^2 - 4\frac{D_2B_3 - B_2D_3}{F_2}\left(C_3\frac{D_2}{F_2} - 2E_3\right)}}{2\left(C_3\frac{D_2}{F_2} - 2E_3\right)}.$$

(H9) $F_2D_2 \neq 0$, $\left(C_3\frac{D_2}{F_2} - 2E_3\right)\left(\frac{E_3B_2 - 2F_3D_2}{F_2} + 2D_3\right) > 0$, $D_2B_3 - B_2D_3 = 0$,
$\rho_0 = -\dfrac{\frac{B_2}{2F_2}\left(C_3\frac{D_2}{F_2} - 2E_3\right) + \frac{E_3B_2 - 2F_3D_2}{F_2} + 2D_3}{\frac{D_2}{F_2}\left(C_3\frac{D_2}{F_2} - 2E_3\right)}$ and $\sigma_0 = \dfrac{\frac{E_3B_2 - 2F_3D_2}{F_2} + 2D_3}{\left(C_3\frac{D_2}{F_2} - 2E_3\right)}$.

(H10) $F_2 = 0$, $D_2 \neq 0$, $0 < 4C_3\left(B_3 - \frac{D_3B_2}{D_2}\right) < \left(2F_3 - \frac{E_3B_2}{D_2}\right)^2$, $\left(2F_3 - \frac{E_3B_2}{D_2}\right) C_3 < 0$, $\rho_0 = \frac{-B_2}{2D_2}$ and $\sigma_0^{\pm} = \dfrac{-\left(2F_3 - \frac{E_3B_2}{D_2}\right) \pm \sqrt{\left(2F_3 - \frac{E_3B_2}{D_2}\right)^2 - 4C_3\left(B_3 - \frac{D_3B_2}{D_2}\right)}}{2C_3}$.

(H11) $F_2D_2 \neq 0$, $0 < -4\frac{B_2D_3 - D_2B_3}{F_2}\left(C_3\frac{D_2}{F_2} - 2E_3\right) < \left(\frac{E_3B_2 - 2F_3D_2}{F_2} + 2D_3\right)^2$,
$\left(C_3\frac{D_2}{F_2} - 2E_3\right)\left(\frac{E_3B_2 - 2F_3D_2}{F_2} + 2D_3\right) > 0$,

$$\rho_0^{\pm} = -\frac{\frac{B_2}{F_2}\left(C_3\frac{D_2}{F_2} - 2E_3\right) + \frac{E_3B_2 - 2F_3D_2}{F_2} + 2D_3 \pm \sqrt{\left(\frac{E_3B_2 - 2F_3D_2}{F_2} + 2D_3\right)^2 + 4\frac{B_2D_3 - D_2B_3}{F_2}\left(C_3\frac{D_2}{F_2} - 2E_3\right)}}{2\frac{D_2}{F_2}\left(C_3\frac{D_2}{F_2} - 2E_3\right)}$$

and

$$\sigma_0^{\pm} = \frac{\frac{E_3B_2 - 2F_3D_2}{F_2} + 2D_3 \pm \sqrt{\left(\frac{E_3B_2 - 2F_3D_2}{F_2} + 2D_3\right)^2 + 4\frac{B_2D_3 - D_2B_3}{F_2}\left(C_3\frac{D_2}{F_2} - 2E_3\right)}}{2\left(C_3\frac{D_2}{F_2} - 2E_3\right)}.$$

We have the following results.

Theorem 2.3. *Let* $\left|\frac{\partial \Theta_1}{\partial x_1}(\zeta(\tau_0))\right| \exp\left(\int_0^{\tau_0} \frac{\partial \mathcal{F}_1(\zeta(r))}{\partial x_1} dr\right) < 1$,
$\left|\frac{\partial \Theta_j}{\partial x_j}(\zeta(\tau_0))\right| \exp\left(\int_0^{\tau_0} \frac{\partial \mathcal{F}_j(\zeta(r))}{\partial x_j} dr\right) = 1$ *for* $j = 2, 3$ *and* $h_0' = 0$.
1) *If one of the hypotheses* **(H1)-(H9)** *is satisfied, then we have a bifurcation of one nontrivial* $(\tau_0 + \bar{\tau}(\alpha))$*-periodic solution of (1.1)-(1.6) with initial condition*

$\Big(x_0 - \frac{b_0'}{a_0'}\alpha - \frac{c_0'}{a_0'}\beta(\alpha) + z_1^*(\bar{\tau}(\alpha), \alpha, \beta(\alpha)), \alpha, \beta(\alpha)\Big)$ for $\alpha > 0$ small enough, where $\bar{\tau}(\alpha) = \rho_0\alpha + o(\alpha)$ and $\beta(\alpha) = \sigma_0\alpha + o(\alpha)$.

2) *If hypotheses* **(H10)** *is satisfied, then we have a bifurcation of two nontrivial $(\tau_0 + \bar{\tau}(\alpha))$-periodic solutions of (1.1)-(1.6) with initial conditions $\Big(x_0 - \frac{b_0'}{a_0'}\alpha - \frac{c_0'}{a_0'}\beta^{\pm}(\alpha) + z_1^*(\bar{\tau}(\alpha), \alpha, \beta^{\pm}(\alpha)), \alpha, \beta^{\pm}(\alpha)\Big)$, where $\bar{\tau}(\alpha) = \rho_0\alpha + o(\alpha)$ and $\beta^{\pm}(\alpha) = \sigma_0^{\pm}\alpha + o(\alpha)$ for $\alpha > 0$ small enough.*

3) *If hypotheses* **(H11)** *is satisfied, then we have a bifurcation of two nontrivial $(\tau_0 + \bar{\tau}^{\pm}(\alpha))$-periodic solutions of (1.1)-(1.6) with initial conditions $\Big(x_0 - \frac{b_0'}{a_0'}\alpha - \frac{c_0'}{a_0'}\beta^{\pm}(\alpha) + z_1^*(\bar{\tau}^{\pm}(\alpha), \alpha, \beta^{\pm}(\alpha)), \alpha, \beta^{\pm}(\alpha)\Big)$, where $\bar{\tau}^{\pm}(\alpha) = \rho_0^{\pm}\alpha + o(\alpha)$ and $\beta^{\pm}(\alpha) = \sigma_0^{\pm}\alpha + o(\alpha)$ for $\alpha > 0$ small enough.*

2.3. **Applications to the pulsed chemotherapy model.** In this section we apply the results obtained above to the following chemotherapeutic model given in [4]

$$\frac{dx_1}{dt} = r_1 x_1 \left(1 - \frac{x_1}{k_1} - \lambda_1(x_2 + x_3)\right), \tag{2.11}$$

$$\frac{dx_2}{dt} = r_2 x_2 \left(1 - \frac{x_2 + x_3}{k_2} - \lambda_2(x_1 + x_3)\right) - m x_2, \tag{2.12}$$

$$\frac{dx_3}{dt} = r_3 x_3 \left(1 - \frac{x_2 + x_3}{k_3} - \lambda_3(x_1 + x_2)\right) + m x_2, \tag{2.13}$$

$$x_1(t_i^+) = T_1 x_1(t_i), \tag{2.14}$$

$$x_2(t_i^+) = (T_2 - R) x_2(t_i), \tag{2.15}$$

$$x_3(t_i^+) = T_3 x_3(t_i) + R x_2(t_i), \tag{2.16}$$

where $t_{i+1} - t_i = \tau > 0, \forall i \in \mathbb{N}$,
The variables and parameters are:
τ: period between two successive drug treatment,
x_j: normal (resp. sensitive tumor and resistant tumor) cells biomass for $j = 1$ (resp. 2,3),
r_j: growth rates of the normal (resp. sensitive tumor and resistant tumor) cells for $j = 1$ (resp. 2,3),
k_j: carrying capacities of the normal (resp. sensitive tumor and resistant tumor) cells for $j = 1$ (resp. 2,3),
λ_j: competitive parameters of the normal (resp. sensitive tumor and resistant tumor) cells for $j = 1$ (resp. 2,3),
T_j: survival fractions of the normal (resp. sensitive tumor and resistant tumor) cells, their values are completely determined by the quantity of injected drugs.
R: Fraction of cells mutating due of the dose of the drug which is less than T_2.
m: acquired resistance parameter usually it is very small.
Note that if $k_2 = k_3$ with $m = 0$ or $R = 0$, then we obtain the models studied in Panetta [5].
The problem (2.11),(2.14), obtained by taking $x_2 = 0$ and $x_3 = 0$, has a τ_0-periodic

solution $x(t,x_0)=x_s(t)$, where

$$x_s(t)=\frac{k_1(T_1-\exp(-r_1\tau_0))\exp(r_1t)}{\exp(r_1t)(T_1-\exp(-r_1\tau_0))+(1-T_1)},\qquad 0<t\leq\tau_0, \tag{2.17}$$

with $x_0=\frac{k_1(T_1-\exp(-r_1\tau_0))}{1-\exp(-r_1\tau_0)}$.

The solution given by (2.17) is defined and stable in the one dimensional space if $T_1>\exp(-r_1\tau_0)$. That is

$$\tau_0>\frac{1}{r_1}\ln\left(\frac{1}{T_1}\right). \tag{2.18}$$

To analyze the bifurcation of nontrivial periodic solutions, first we calculate e_0', i_0' and h_0'.

We have $e_0'=1-\frac{(T_2-R)\exp(r_2\tau_0)}{T_1^{\frac{\lambda_2r_2k_1}{r_1}}\exp(r_2\lambda_2k_1+m)\tau_0}$, $i_0'=1-\frac{T_3\exp(r_3\tau_0)}{T_1^{\frac{\lambda_3r_3k_1}{r_1}}\exp(r_3\lambda_3k_1\tau_0)}$ and

$h_0'=-\frac{R\exp((r_2(1-\lambda_2k_1)-m)\tau_0)}{T_1^{\frac{\lambda_2r_2k_1}{r_1}}}-\frac{T_3m\exp(r_3(1-\lambda_3k_1)\tau_0)\int_0^{\tau_0}\exp(-m\mu)I_2(\mu)I_3^{-1}(\mu)d\mu}{T_1^{\frac{\lambda_3r_3k_1}{r_1}}(1-\exp(-r_1\tau_0))^{\frac{-\lambda_2r_2k_1}{r_1}+\frac{\lambda_3r_3k_1}{r_1}}}\leq 0$,

where

$I_j(\mu)=\exp(r_j\mu)[(T_1-\exp(-r_1\tau_0))\exp(r_1\mu)+(1-T_1)]^{-\frac{\lambda_jr_jk_1}{r_1}}\neq 0$ for $j=2,3$.

We consider the case $e_0'=i_0'=0$. That is

$$(r_2(1-\lambda_2k_1)-m)\tau_0=\ln(T_1^{\frac{\lambda_2r_2k_1}{r_1}}(T_2-R)^{-1}) \tag{2.19}$$

and

$$(r_3(1-\lambda_3k_1))\tau_0=\ln(T_1^{\frac{\lambda_3r_3k_1}{r_1}}T_3^{-1}). \tag{2.20}$$

From (2.18), (2.19) and (2.20) we deduce several cases for possible bifurcation of nontrivial periodic solutions:

(B1) $\lambda_2<\frac{r_2-m}{r_2k_1}$, $\lambda_3<\frac{1}{k_1}$, $T_2=T_1^{-\frac{\lambda_2r_2k_1-\lambda_3k_1(r_2-m)}{r_1(1-\lambda_3k_1)}}T_3^{-\frac{r_2(1-\lambda_2k_1)-m}{r_3(1-\lambda_3k_1)}}+R$, $T_3<T_1^{\frac{\lambda_3r_3k_1}{r_1}}$ and $\tau_0=\frac{\ln(T_1^{\frac{\lambda_2r_2k_1}{r_1}}(T_2-R)^{-1})}{r_2(1-\lambda_2k_1)-m}$.

(B2) $\lambda_2<\frac{r_2-m}{r_2k_1}$, $\lambda_3=\frac{1}{k_1}$, $T_2<T_1^{\frac{\lambda_2r_2k_1}{r_1}}+R$, $T_3=T_1^{\frac{r_3}{r_1}}$ and $\tau_0=\frac{\ln(T_1^{\frac{\lambda_2r_2k_1}{r_1}}(T_2-R)^{-1})}{r_2(1-\lambda_2k_1)-m}$.

(B3) $\lambda_2=\frac{r_2-m}{r_2k_1}$, $\lambda_3<\frac{1}{k_1}$, $T_2=T_1^{\frac{r_2-m}{r_1}}+R$, $T_3<T_1^{\frac{\lambda_3r_3k_1}{r_1}}$ and $\tau_0=\frac{\ln(T_1^{\frac{\lambda_3r_3k_1}{r_1}}T_3^{-1})}{r_3(1-\lambda_3k_1)}$.

(B4) $\lambda_2=\frac{r_2-m}{r_2k_1}$, $\lambda_3=\frac{1}{k_1}$, $T_2=T_1^{\frac{r_2-m}{r_1}}+R$, $T_3=T_1^{\frac{r_3}{r_1}}$ and $\tau_0>\frac{1}{r_1}\ln\left(\frac{1}{T_1}\right)$.

Suppose that either **(B3)** or **(B4)** is satisfied, then $\mathcal{B}_2=0$. If in addition $R+m\neq 0$ and $\lambda_2=\lambda_3=0$, we obtain $h_0'=-Re^{(r_2-m)\tau_0}-mT_3e^{r_3\tau_0}\left(\frac{e^{(r_2-r_3-m)\tau_0}-1}{r_2-r_3-m}\right)<0$,

$\mathcal{D}_2=2(T_2-R)T_3e^{r_3\tau_0}e^{(r_2-m)\tau_0}(e^{r_3\tau_0}-1)h_0'^{-1}\left(\frac{r_2}{k_2}+\frac{r_2-m}{k_3}\right)<0$, and

$\mathcal{C}_2=-6(T_2-R)T_3r_2r_3^{-1}k_2^{-1}k_3^{-1}e^{r_3\tau_0}e^{(r_2-m)\tau_0}(e^{r_3\tau_0}-1)^2h_0'^{-1}>0$.

From theorem 2.1, we deduce the following result.

Corollary 2.1. *If either* **(B3)** *or* **(B4)** *holds, and $R+m\neq 0$ then we have a bifurcation of one nontrivial $\tau(\alpha)$-periodic solution of (2.11)-(2.16) with initial condition* $\left(x_0-\frac{c_0'}{a_0'}\alpha+z_1^*(\bar\tau(\alpha),\alpha),z_2^*(\bar\tau(\alpha),\alpha),\alpha\right)$ *and period $\tau(\alpha)=\tau_0+\bar\tau(\alpha)$ for $\alpha(>0)$, λ_2 and λ_3 small enough where $z_2^*(\bar\tau(\alpha),\alpha)=-\frac{1}{2}T_3k_3^{-1}e^{r_3\tau_0}h_0'^{-1}(e^{r_3\tau_0}-1)\alpha^2+o(|\alpha|^2)$*

and
$\bar{\tau}(\alpha) = \frac{3(e^{r_3\tau_0}-1)}{2r_3k_3}\alpha + o(|\alpha|)$.

Suppose that either **(B1)** or **(B2)** holds. Then for $R+m \neq 0$ and $\lambda_2 = \lambda_3 = 0$, we have
$$0 > h_0' = \begin{cases} -Re^{(r_2-m)\tau_0} - mT_3e^{r_3\tau_0}\left(\frac{e^{(r_2-r_3-m)\tau_0}-1}{r_2-r_3-m}\right), & \text{for} \quad r_2-r_3-m \neq 0, \\ -Re^{(r_2-m)\tau_0} - mT_3e^{r_3\tau_0}\tau_0, & \text{for} \quad r_2-r_3-m = 0, \end{cases}$$
$\mathcal{D}_2 = 2(T_2-R)T_3e^{r_3\tau_0}e^{(r_2-m)\tau_0}(e^{r_3\tau_0}-1)h_0'^{-1}\left(\frac{r_2}{k_2}+\frac{r_2-m}{k_3}\right) < 0$,
$\mathcal{B}_2 = -2(T_2-R)T_3(r_2-m)r_3e^{r_3\tau_0}e^{(r_2-m)\tau_0}h_0'^{-1} > 0$, and
$\mathcal{C}_2 = -6(T_2-R)T_3r_2r_3^{-1}k_2^{-1}k_3^{-1}e^{r_3\tau_0}e^{(r_2-m)\tau_0}(e^{r_3\tau_0}-1)^2h_0'^{-1} > 0$.
Then for $k_3 \neq \frac{(r_2-m)k_2}{r_2}$ we have $0 \neq B_2C_2 < \frac{3}{4}C_3^2$.
From theorem 2.2, we deduce the following results.

Corollary 2.2. *If either* **(B1)** *or* **(B2)** *holds, and $R+m\neq 0$ then*
1) *for $\frac{(r_2-m)k_2}{r_2} \neq k_3 < \frac{2(r_2-m)k_2}{r_2}$, we have a bifurcation of two nontrivial periodic solutions of (2.11)-(2.16) with initial conditions* $\left(x_0 - \frac{c_0'}{a_0'}\alpha + z_1^*(\bar{\tau}^{\pm}(\alpha),\alpha), z_2^*(\bar{\tau}^{\pm}(\alpha),\alpha),\alpha\right)$ *and periods $\tau^{\pm}(\alpha) = \tau_0 + \bar{\tau}^{\pm}(\alpha)$ for $\alpha(>0)$, λ_2 and λ_3 small enough where $\bar{\tau}^{+}(\alpha) = \frac{(e^{r_3\tau_0}-1)}{r_3k_3}\alpha + o(|\alpha|)$, $z_2^*(\bar{\tau}^{+}(\alpha),\alpha) = -2T_3k_3^{-1}e^{r_3\tau_0}(e^{r_3\tau_0}-1)h_0'^{-1}\alpha^2 + o(|\alpha|^2)$, $\bar{\tau}^{-}(\alpha) = \frac{(e^{r_3\tau_0}-1)r_2}{(r_2-m)r_3k_2}\alpha + o(|\alpha|)$ and* $z_2^*(\bar{\tau}^{-}(\alpha),\alpha) = \frac{T_3e^{r_3\tau_0}h_0'^{-1}(e^{r_3\tau_0}-1)(r_2k_3-2(r_2-m)k_2)}{(r_2-m)k_2k_3}\alpha^2 + o(|\alpha|^2)$.
2) *for $k_3 > \frac{2(r_2-m)k_2}{r_2}$, we have a bifurcation of one nontrivial periodic solution of (2.11)-(2.16) with initial condition $\left(x_0 - \frac{c_0'}{a_0'}\alpha + z_1^*(\bar{\tau}^{+}(\alpha),\alpha), z_2^*(\bar{\tau}^{+}(\alpha),\alpha),\alpha\right)$ and period $\tau^{+}(\alpha) = \tau_0 + \bar{\tau}^{+}(\alpha)$ for $\alpha(>0)$, λ_2 and λ_3 small enough where $\bar{\tau}^{+}(\alpha) = \frac{(e^{r_3\tau_0}-1)}{r_3k_3}\alpha + o(|\alpha|)$ and $z_2^*(\bar{\tau}^{+}(\alpha),\alpha) = -2T_3k_3^{-1}e^{r_3\tau_0}(e^{r_3\tau_0}-1)h_0'^{-1}\alpha^2 + o(|\alpha|^2)$.*

Suppose that **(B1)** is satisfied. Then for $R = m = 0$ we have $h_0' = B_3 = D_3 = 0$. If in addition $\lambda_1 = 0$ then we obtain
$B_2 = 2T_2r_2k_2^{-1}e^{r_2(1-\lambda_2k_1)\tau_0}T_1^{-\frac{\lambda_2r_2k_1}{r_1}}(1-e^{-r_1\tau_0})^{\frac{\lambda_2r_2k_1}{r_1}}\int_0^{\tau_0}I_2(\mu)d\mu > 0$,
$D_2 = -T_2r_2(1-\lambda_2k_1)T_1^{-\frac{\lambda_2r_2k_1}{r_1}}e^{r_2(1-\lambda_2k_1)\tau_0} < 0$,
$F_2 = T_2r_2e^{r_2(1-\lambda_2k_1)\tau_0}(1-e^{-r_1\tau_0})^{\frac{\lambda_3r_3k_1}{r_1}}T_1^{-\frac{\lambda_2r_2k_1}{r_1}}(\frac{1}{k_2}+\lambda_2)\int_0^{\tau_0}I_3(\mu)d\mu > 0$,
$C_3 = T_3\frac{2r_3}{k_3}e^{r_3(1-\lambda_3k_1)\tau_0}T_1^{-\frac{\lambda_3r_3k_1}{r_1}}(1-e^{-r_1\tau_0})^{\frac{\lambda_3r_3k_1}{r_1}}\int_0^{\tau_0}I_3(\mu)d\mu > 0$,
$E_3 = -T_3r_3T_1^{\frac{-\lambda_3r_3k_1}{r_1}}e^{r_3(1-\lambda_3k_1)\tau_0}(1-\lambda_3k_1) < 0$, and
$F_3 = T_3r_3e^{r_3(1-\lambda_3k_1)\tau_0}(1-e^{-r_1\tau_0})^{\frac{\lambda_2r_2k_1}{r_1}}T_1^{-\frac{\lambda_3r_3k_1}{r_1}}(\frac{1}{k_3}+\lambda_3)\int_0^{\tau_0}I_2(\mu)d\mu > 0$.
To have the conditions of **(H9)** we need $\left(\frac{C_3D_2}{2F_2}-E_3\right)\left(\frac{E_3B_2-2F_3D_2}{F_2}\right) > 0$. The last inequality is satisfied if one of the following assumptions holds:
(C1) $\frac{k_3-k_2(1-\lambda_2k_1)}{(k_1+(1-\lambda_2k_1)k_2)k_3} < \lambda_3 < \frac{1}{k_1} - \frac{(1-\lambda_2k_1)k_2}{(1+\lambda_2k_2)k_1k_3}$ and $k_2 \leq k_3$.
(C2) $\lambda_3 < \frac{1}{k_1} - \frac{(1-\lambda_2k_1)k_2}{(1+\lambda_2k_2)k_1k_3}$, $\frac{k_2-k_3}{k_2(k_1+k_3)} < \lambda_2 \leq \frac{1}{k_1} - \frac{k_3}{k_2k_1}$ and $k_2 > k_3$.
(C3) $\frac{k_3-k_2(1-\lambda_2k_1)}{(k_1+(1-\lambda_2k_1)k_2)k_3} < \lambda_3 < \frac{1}{k_1} - \frac{(1-\lambda_2k_1)k_2}{(1+\lambda_2k_2)k_1k_3}$, $\frac{1}{k_1} - \frac{k_3}{k_2k_1} < \lambda_2 < \frac{1}{k_1}$ and $k_2 > k_3$.
From theorem 2.3, we deduce the following results.

Corollary 2.3. *If* **(B1)** *and* **(C1)** *hold with $R = m = 0$, then we have a bifurcation of one nontrivial $\tau(\alpha)$-periodic solution of (2.11)-(2.16) with initial condition*

$\left(x_0 - \frac{b_0'}{a_0'}\alpha - \frac{b_0'}{a_0'}\beta(\alpha) + z_1^*(\bar{\tau}(\alpha), \alpha, \beta(\alpha)), \alpha, \beta(\alpha)\right)$ *and period* $\tau(\alpha) = \tau_0 + \bar{\tau}(\alpha)$ *for* $\alpha(> 0)$ *and* λ_1 *small enough where*

$$\bar{\tau}(\alpha) = \left(\frac{[1-(1+\lambda_2 k_2)(1+k_3\lambda_3)](1-e^{-r_1\tau_0})^{\frac{\lambda_2 r_2 k_1}{r_1}} \int_0^{\tau_0} I_2(\mu)d\mu}{[(1-\lambda_2 k_1)k_2-(1-\lambda_3 k_1)(1+\lambda_2 k_2)k_3]} \right) \alpha + o(|\alpha|) \text{ and}$$

$$\beta(\alpha) = \left(\frac{(1-e^{-r_1\tau_0})^{\frac{(\lambda_2 r_2-\lambda_3 r_3)k_1}{r_1}} [(1-\lambda_3 k_1)k_3-k_2(1-\lambda_2 k_1)(1+k_3\lambda_3)] \int_0^{\tau_0} I_2(\mu)d\mu}{[(1-\lambda_2 k_1)k_2-(1-\lambda_3 k_1)(1+\lambda_2 k_2)k_3] \int_0^{\tau_0} I_3(\mu)d\mu} \right) \alpha + o(|\alpha|).$$

Corollary 2.4. *If* **(B1)** *and* **(C2)** *hold with* $R = m = 0$, *then we have the same result as in corollary 2.3 .*

Corollary 2.5. *If* **(B1)** *and* **(C3)** *hold with* $R = m = 0$, *then we have the same result as in corollary 2.3 .*

3. Concluding remarks

The model studied here is inspired from [4], where the authors study only two cases **(C1)** and **(C2)** but the case **(C3)** is undetermined. In this work the degenerate cases corresponding to $e_0' = i_0' = 0$ (*i.e.* **(C3)**) are considered. The trivial solution x_s is assumed stable in the one dimensional space ($a_0' \neq 0$) and the trivial solution $(x_s, 0, 0)$ is stable in three dimensional space for spectral radius of $D_X\Psi(\tau_0, X_0)$ less than one ($e_0' \neq 0$ and $i_0' \neq 0$). The cases $e_0' = i_0' = 0$ correspond to the lost of stability of the trivial solution, in these cases we investigate the bifurcation of nontrivial periodic solutions by the mean of Lyapunov-Schmidt method. The analysis of bifurcation is based on the study of the matrix E and it's determinant $det(E) = a_0'e_0'i_0'$, especially on the elements $a_0'(\neq 0)$, $e_0'(= 0)$ and $i_0'(= 0)$. For $h_0' \neq 0$, we determine the case of bifurcation of one (Theorem 2.1) or two (Theorem 2.2) nontrivial periodic solutions. For $h_0' = 0$, we give all possible cases of bifurcation in the hypotheses **(H1)-(H11)**, the other situations correspond to undetermined cases. Each hypotheses of **(H1)-(H9)** gives bifurcation of one nontrivial periodic solution (Theorem 2.3, 1)), the hypotheses **(H10)** gives bifurcation of two nontrivial solutions with the same period and different initial conditions (Theorem 2.3, 2)), and the hypotheses **(H11)** corresponds to two nontrivial periodic solutions with different periods (Theorem 2.3, 3)). The results obtained are applied to the model in [4] and to the particular cases ($k_2 = k_3,\ R = 0$ or $m = 0$) corresponding to the models in [5] (Corollaries 2.1, 2.2 and 2.3). We have studied the bifurcation of nontrivial periodic solutions for the model (2.11)-(2.16) with respect to the competition parameters $\lambda_j, j = 1, 2, 3$. Note that the methods used in this work could be applied for other similar models from population dynamics. Other situations like the case of many drugs (see for instance [6],[3]) could be very interesting to be considered.

4. Appendix A

The results of this section are obtained from [4].

4.1. **First partial derivatives of $\Phi = (\Phi_1, \Phi_2, \Phi_3)$.** For $t \in (0, \tau)$, we have

$\frac{\partial \Phi_2}{\partial x_1}(t, X_0) = 0$, $\frac{\partial \Phi_2}{\partial x_3}(t, X_0) = 0$, $\frac{\partial \Phi_3}{\partial x_1}(t, X_0) = 0$, $\frac{\partial \Phi_1}{\partial x_1}(t, X_0) = \exp\left(\int_0^t \frac{\partial \mathcal{F}_1(\zeta(r))}{\partial x_1} dr\right)$,

$\frac{\partial \Phi_2}{\partial x_2}(t, X_0) = \exp\left(\int_0^t \frac{\partial \mathcal{F}_2(\zeta(r))}{\partial x_2} dr\right)$, $\frac{\partial \Phi_3}{\partial x_3}(t, X_0) = \exp\left(\int_0^t \frac{\partial \mathcal{F}_3(\zeta(r))}{\partial x_3} dr\right)$,

$$\frac{\partial\Phi_1}{\partial x_2}(t,X_0)=\int_0^t \exp\left(\int_\mu^t \frac{\partial\mathcal{F}_1(\zeta(r))}{\partial x_1}dr\right)\left[\frac{\partial\mathcal{F}_1(\zeta(\mu))}{\partial x_2}\exp\left(\int_0^\mu \frac{\partial\mathcal{F}_2(\zeta(r))}{\partial x_2}dr\right)d\mu\right.$$
$$\left.+\ \frac{\partial\mathcal{F}_1(\zeta(\mu))}{\partial x_3}\int_0^\mu \exp\left(\int_s^\mu \frac{\partial\mathcal{F}_3(\zeta(r))}{\partial x_3}dr\right)\frac{\partial\mathcal{F}_3(\zeta(s))}{\partial x_2}\exp\left(\int_0^s \frac{\partial\mathcal{F}_2(\zeta(r))}{\partial x_2}dr\right)ds\right]d\mu,$$
$$\frac{\partial\Phi_1}{\partial x_3}(t,X_0)=\int_0^t \exp\left(\int_\mu^t \frac{\partial\mathcal{F}_1(\zeta(r))}{\partial x_1}dr\right)\frac{\partial\mathcal{F}_1(\zeta(\mu))}{\partial x_3}\exp\left(\int_0^\mu \frac{\partial\mathcal{F}_3(\zeta(r))}{\partial x_3}dr\right)d\mu \text{ and}$$
$$\frac{\partial\Phi_3}{\partial x_2}(t,X_0)=\int_0^t \exp\left(\int_\mu^t \frac{\partial\mathcal{F}_3(\zeta(r))}{\partial x_3}dr\right)\frac{\partial\mathcal{F}_3(\zeta(\mu))}{\partial x_2}\exp\left(\int_0^\mu \frac{\partial\mathcal{F}_2(\zeta(r))}{\partial x_2}dr\right)d\mu.$$

4.2. **Second partial derivatives of $\Phi=(\Phi_1,\Phi_2,\Phi_3)$.** For $t\in(0,\tau)$, we have $\frac{\partial^2\Phi_2}{\partial x_1^2}(t,X_0)=0$, $\frac{\partial^2\Phi_2}{\partial x_1\partial x_3}(t,X_0)=0$, $\frac{\partial^2\Phi_2}{\partial x_3^2}(t,X_0)=0$, $\frac{\partial^2\Phi_3}{\partial x_1^2}(t,X_0)=0$,

$$\frac{\partial^2\Phi_2}{\partial x_1\partial x_2}(t,X_0)=\exp\left(\int_0^t \frac{\partial\mathcal{F}_2(\zeta(r))dr}{\partial x_2}\right)\int_0^t \frac{\partial^2\mathcal{F}_2(\zeta(\mu))}{\partial x_1\partial x_2}\exp\left(\int_0^\mu \frac{\partial\mathcal{F}_1(\zeta(r))dr}{\partial x_1}\right)d\mu,$$
$$\frac{\partial^2\Phi_2}{\partial x_2^2}(t,X_0)=\exp\left(\int_0^t \frac{\partial\mathcal{F}_2(\zeta(r))dr}{\partial x_2}\right)\int_0^t\left[2\frac{\partial^2\mathcal{F}_2(\zeta(\mu))}{\partial x_1\partial x_2}\frac{\partial\Phi_1(\mu,X_0)}{\partial x_2}+\frac{\partial^2\mathcal{F}_2(\zeta(\mu))}{\partial x_2^2}\frac{\partial\Phi_2(\mu,X_0)}{\partial x_2}\right.$$
$$\left.+\ 2\frac{\partial^2\mathcal{F}_2(\zeta(\mu))}{\partial x_2\partial x_3}\frac{\partial\Phi_3(\mu,X_0)}{\partial x_2}\right]d\mu,$$
$$\frac{\partial^2\Phi_2}{\partial x_3\partial x_2}(t,X_0)=\exp\left(\int_0^t \frac{\partial\mathcal{F}_2(\zeta(r))dr}{\partial x_2}\right)\int_0^t\left[\frac{\partial^2\mathcal{F}_2(\zeta(\mu))}{\partial x_2\partial x_3}\exp\left(\int_0^\mu \frac{\partial\mathcal{F}_3(\zeta(r))dr}{\partial x_3}\right)\right.$$
$$\left.+\ \frac{\partial^2\mathcal{F}_2(\zeta(\mu))}{\partial x_1\partial x_2}\frac{\partial\Phi_1(\mu,X_0)}{\partial x_3}\right]d\mu,$$
$$\frac{\partial^2\Phi_3}{\partial x_1\partial x_3}(t,X_0)=\exp\left(\int_0^t \frac{\partial\mathcal{F}_3(\zeta(r))dr}{\partial x_3}\right)\int_0^t \frac{\partial^2\mathcal{F}_3(\zeta(\mu))}{\partial x_1\partial x_3}\exp\left(\int_0^\mu \frac{\partial\mathcal{F}_1(\zeta(r))dr}{\partial x_1}\right)d\mu,$$
$$\frac{\partial^2\Phi_3}{\partial x_3^2}(t,X_0)=\exp\left(\int_0^t \frac{\partial\mathcal{F}_3(\zeta(r))dr}{\partial x_3}\right)\int_0^t\left[\frac{\partial^2\mathcal{F}_3(\zeta(\mu))}{\partial x_3^2}\exp\left(\int_0^\mu \frac{\partial\mathcal{F}_3(\zeta(r))dr}{\partial x_3}\right)\right.$$
$$\left.+2\frac{\partial^2\mathcal{F}_3(\zeta(\mu))}{\partial x_1\partial x_3}\frac{\partial\Phi_1(\mu,X_0)}{\partial x_3}\right]d\mu,$$
$$\frac{\partial^2\Phi_3}{\partial x_1\partial x_2}(t,X_0)=\int_0^t \exp\left(\int_\mu^t \frac{\partial\mathcal{F}_3(\zeta(r))dr}{\partial x_3}\right)\left[\frac{\partial^2\mathcal{F}_3(\zeta(\mu))}{\partial x_1\partial x_2}\frac{\partial\Phi_1(\mu,X_0)}{\partial x_1}\frac{\partial\Phi_2(\mu,X_0)}{\partial x_2}\right.$$
$$\left.+\ \frac{\partial\mathcal{F}_3(\zeta(\mu))}{\partial x_2}\frac{\partial^2\Phi_2(\mu,X_0)}{\partial x_1\partial x_2}+\frac{\partial^2\mathcal{F}_3(\zeta(\mu))}{\partial x_1\partial x_3}\frac{\partial\Phi_1(\mu,X_0)}{\partial x_1}\frac{\partial\Phi_3(\mu,X_0)}{\partial x_2}\right]d\mu,$$
$$\frac{\partial^2\Phi_3}{\partial x_2^2}(t,X_0)=\int_0^t \exp\left(\int_\mu^t \frac{\partial\mathcal{F}_3(\zeta(r))dr}{\partial x_3}\right)\left[2\frac{\partial^2\mathcal{F}_3(\zeta(\mu))}{\partial x_1\partial x_2}\frac{\partial\Phi_1(\mu,X_0)}{\partial x_2}\frac{\partial\Phi_2(\mu,X_0)}{\partial x_2}\right.$$
$$+\frac{\partial^2\mathcal{F}_3(\zeta(\mu))}{\partial x_2^2}\left(\frac{\partial\Phi_2(\mu,X_0)}{\partial x_2}\right)^2+2\frac{\partial^2\mathcal{F}_3(\zeta(\mu))}{\partial x_2\partial x_3}\frac{\partial\Phi_3(\mu,X_0)}{\partial x_2}\frac{\partial\Phi_2(\mu,X_0)}{\partial x_2}+\frac{\partial\mathcal{F}_3(\zeta(\mu))}{\partial x_2}\frac{\partial^2\Phi_2(\mu,X_0)}{\partial x_2^2}$$
$$\left.+2\frac{\partial^2\mathcal{F}_3(\zeta(\mu))}{\partial x_1\partial x_3}\frac{\partial\Phi_1(\mu,X_0)}{\partial x_2}\frac{\partial\Phi_3(\mu,X_0)}{\partial x_2}+\frac{\partial^2\mathcal{F}_3(\zeta(\mu))}{\partial x_3^2}\left(\frac{\partial\Phi_3(\mu,X_0)}{\partial x_2}\right)^2\right]d\mu, \text{ and}$$
$$\frac{\partial^2\Phi_3}{\partial x_3\partial x_2}(t,X_0)=\int_0^t \exp\left(\int_\mu^t \frac{\partial\mathcal{F}_3(\zeta(r))dr}{\partial x_3}\right)\left[\frac{\partial^2\mathcal{F}_3(\zeta(\mu))}{\partial x_3\partial x_1}\frac{\partial\Phi_1(\mu,X_0)}{\partial x_2}\frac{\partial\Phi_3(\mu,X_0)}{\partial x_3}\right.$$
$$+\left(\frac{\partial^2\mathcal{F}_3(\zeta(\mu))}{\partial x_1\partial x_2}\frac{\partial\Phi_1(\mu,X_0)}{\partial x_3}+\frac{\partial^2\mathcal{F}_3(\zeta(\mu))}{\partial x_3\partial x_2}\frac{\partial\Phi_3(\mu,X_0)}{\partial x_3}\right)\frac{\partial\Phi_2(\mu,X_0)}{\partial x_2}+\frac{\partial\mathcal{F}_3(\zeta(\mu))}{\partial x_2}\frac{\partial^2\Phi_2(\mu,X_0)}{\partial x_3\partial x_2}$$
$$\left.+\left(\frac{\partial^2\mathcal{F}_3(\zeta(\mu))}{\partial x_3^2}\frac{\partial\Phi_3(\mu,X_0)}{\partial x_3}+\frac{\partial^2\mathcal{F}_3(\zeta(\mu))}{\partial x_1\partial x_3}\frac{\partial\Phi_1(\mu,X_0)}{\partial x_3}\right)\frac{\partial\Phi_3(\mu,X_0)}{\partial x_2}\right]d\mu.$$

5. Appendix B: Case $h_0'\neq 0$

Let $\eta_0(\bar\tau)=\tau_0+\bar\tau$, $\eta_1(\bar\tau,\alpha)=x_0-\frac{c_0'}{a_0'}\alpha+\mathsf{z}_1^*(\bar\tau,\alpha)$, $\eta_2(\bar\tau,\alpha)=\mathsf{z}_2^*(\bar\tau,\alpha)$, $\eta_3(\bar\tau,\alpha)=\alpha$, $\eta=(\eta_0,\eta_1,\eta_2,\eta_3)$, $\mathcal{Y}_0=(y_1,y_2,y_3)$, $y_1=-\frac{c_0'}{a_0'}$, $y_2=0$ and $y_3=1$.

5.1. **First and second partial derivatives of $\mathcal{Z}^* = (\mathbf{z}_1^*, \mathbf{z}_2^*, 0)$.** From the first and second partial derivatives of equations (2.2) and (2.3), we obtain

$\frac{\partial \mathsf{z}_1^*}{\partial \bar{\tau}}(0,0) = a_0'^{-1} \frac{\partial \Theta_1(\Phi(\tau_0,X_0))}{\partial x_1} \frac{\partial \Phi_1(\tau_0,X_0)}{\partial \bar{\tau}}$, $\frac{\partial \mathsf{z}_2^*}{\partial \bar{\tau}}(0,0) = 0$, $\frac{\partial \mathsf{z}_1^*}{\partial \alpha}(0,0) = 0$, $\frac{\partial \mathsf{z}_2^*}{\partial \alpha}(0,0) = 0$,

$$\begin{aligned}\frac{\partial^2 \mathsf{z}_2^*}{\partial \bar{\tau}\partial \alpha}(0,0) &= h_0'^{-1} \frac{\partial \mathsf{z}_1^*(0,0)}{\partial \bar{\tau}} \left(\frac{\partial^2 \Theta_3(\Phi(\tau_0,X_0))}{\partial x_1 \partial x_3} \frac{\partial \Phi_1(\tau_0,X_0)}{\partial x_1} + \frac{\partial^2 \Phi_3(\tau_0,X_0)}{\partial x_1 \partial x_3} \right) \frac{\partial \Theta_3(\Phi(\tau_0,X_0))}{\partial x_3} \\ &+ h_0'^{-1} \left(\frac{\partial^2 \Theta_3(\Phi(\tau_0,X_0))}{\partial x_1 \partial x_3} \frac{\partial \Phi_1(\tau_0,X_0)}{\partial \bar{\tau}} \frac{\partial \Phi_3(\tau_0,X_0)}{\partial x_3} + \frac{\partial \Theta_3(\Phi(\tau_0,X_0))}{\partial x_3} \frac{\partial^2 \Phi_3(\tau_0,X_0)}{\partial \bar{\tau}\partial x_3} \right),\end{aligned}$$

$$\begin{aligned}\frac{\partial^2 \mathsf{z}_2^*}{\partial \alpha^2}(0,0) = h_0'^{-1} \Bigg[& 2 \left(\frac{\partial \Phi_1(\tau_0,X_0)}{\partial x_3} - \frac{\partial \Phi_1(\tau_0,X_0)}{\partial x_1} \frac{c_0'}{a_0'} \right) \frac{\partial^2 \Theta_3(\Phi(\tau_0,X_0))}{\partial x_1 \partial x_3} \frac{\partial \Phi_3(\tau_0,X_0)}{\partial x_3} \\ & + \frac{\partial^2 \Theta_3(\Phi(\tau_0,X_0))}{\partial x_3^2} \left(\frac{\partial \Phi_3(\tau_0,X_0)}{\partial x_3} \right)^2 + \left(\frac{\partial^2 \Phi_3(\tau_0,X_0)}{\partial x_3^2} - 2 \frac{\partial^2 \Phi_3(\tau_0,X_0)}{\partial x_1 \partial x_3} \frac{c_0'}{a_0'} \right) \frac{\partial \Theta_3(\Phi(\tau_0,X_0))}{\partial x_3} \Bigg].\end{aligned}$$

5.2. **First partial derivatives of f_2.**

$$\frac{\partial \mathsf{f}_2}{\partial \bar{\tau}}(\bar{\tau},\alpha) = \frac{\partial}{\partial \bar{\tau}} \left(\eta_2 - \Theta_2 \circ \Phi(\eta) \right)(\bar{\tau},\alpha) = \left[\frac{\partial \mathsf{z}_2^*}{\partial \bar{\tau}} - \sum_{i=1}^{3} \frac{\partial \Theta_2(\Phi(\eta))}{\partial x_i} \frac{\partial}{\partial \bar{\tau}} \Phi_i(\eta) \right](\bar{\tau},\alpha),$$

where $\frac{\partial}{\partial \bar{\tau}} \Phi_i(\eta)(\bar{\tau},\alpha) = \left[\frac{\partial \Phi_i(\eta)}{\partial \bar{\tau}} + \sum_{j=1}^{3} \frac{\partial \Phi_i(\eta)}{\partial x_j} \frac{\partial \mathsf{z}_j^*}{\partial \bar{\tau}} \right](\bar{\tau},\alpha).$

Since $\frac{\partial \Theta_2(\Phi(\eta))}{\partial x_1}(0,0) = \frac{\partial \Theta_2(\Phi(\eta))}{\partial x_3}(0,0) = 0$, $\frac{\partial \Phi_2(\eta)}{\partial x_1}(0,0) = \frac{\partial \Phi_2(\eta)}{\partial x_3} = 0$, $\frac{\partial \Phi_2(\eta)}{\partial \bar{\tau}}(0,0) = 0$ and $\frac{\partial \mathsf{z}_2^*}{\partial \bar{\tau}}(0,0) = 0$, we obtain $\frac{\partial \mathsf{f}_2}{\partial \bar{\tau}}(0,0) = 0$.

On the other hand, $\frac{\partial \mathsf{f}_2}{\partial \alpha}(\bar{\tau},\alpha) = \left[\frac{\partial \mathsf{z}_2^*}{\partial \alpha} - \sum_{i=1}^{3} \frac{\partial \Theta_2(\Phi(\eta))}{\partial x_i} \frac{\partial}{\partial \alpha} \Phi_i(\eta) \right](\bar{\tau},\alpha),$

where $\frac{\partial}{\partial \alpha} \Phi_i(\eta)(\bar{\tau},\alpha) = \left[\sum_{j=1}^{3} \frac{\partial \Phi_i(\eta)}{\partial x_j} \left(y_j + \frac{\partial \mathsf{z}_j^*}{\partial \alpha} \right) \right](\bar{\tau},\alpha).$

Since $\frac{\partial \Theta_2(\Phi(\eta))}{\partial x_1}(0,0) = \frac{\partial \Theta_2(\Phi(\eta))}{\partial x_3}(0,0) = 0$, $\frac{\partial \Phi_2(\eta)}{\partial x_1}(0,0) = \frac{\partial \Phi_2(\eta)}{\partial x_3}(0,0) = 0$, and $\frac{\partial \mathsf{z}_2^*}{\partial \alpha}(0,0) = 0$, we obtain $\frac{\partial \mathsf{f}_2}{\partial \alpha}(0,0) = 0$.

5.3. **Second partial derivatives of f_2.**

$$\frac{\partial^2 \mathsf{f}_2}{\partial \bar{\tau}^2}(\bar{\tau},\alpha) = \left[\frac{\partial^2 \mathsf{z}_2^*}{\partial \bar{\tau}^2} - \sum_{j=1}^{3} \sum_{i=1}^{3} \frac{\partial^2 \Theta_2(\Phi(\eta))}{\partial x_i \partial x_j} \frac{\partial}{\partial \bar{\tau}} \Phi_i(\eta) \frac{\partial}{\partial \bar{\tau}} \Phi_j(\eta) - \sum_{i=1}^{3} \frac{\partial \Theta_2(\Phi(\eta))}{\partial x_i} \frac{\partial^2}{\partial \bar{\tau}^2} \Phi_i(\eta) \right](\bar{\tau},\alpha),$$

$$\begin{aligned}\text{where } \frac{\partial^2}{\partial \bar{\tau}^2} \Phi_i(\eta)(\bar{\tau},\alpha) = \Bigg[& \frac{\partial^2 \Phi_i(\eta)}{\partial \bar{\tau}^2} + 2 \sum_{j=1}^{3} \frac{\partial^2 \Phi_i(\eta)}{\partial \bar{\tau} \partial x_j} \frac{\partial \mathsf{z}_j^*}{\partial \bar{\tau}} + \sum_{j=1}^{3} \sum_{k=1}^{3} \frac{\partial^2 \Phi_i(\eta)}{\partial x_j \partial x_k} \frac{\partial \mathsf{z}_j^*}{\partial \bar{\tau}} \frac{\partial \mathsf{z}_k^*}{\partial \bar{\tau}} \\ & + \sum_{j=1}^{3} \frac{\partial \Phi_i(\eta)}{\partial x_j} \frac{\partial^2 \mathsf{z}_j^*}{\partial \bar{\tau}^2} \Bigg](\bar{\tau},\alpha).\end{aligned}$$

We obtain $\frac{\partial^2 \mathsf{f}_2}{\partial \bar{\tau}^2}(0,0) = \frac{\partial^2 \mathsf{z}_2^*(0,0)}{\partial \bar{\tau}^2} \left(1 - \frac{\partial \Theta_2(\Phi(\tau_0,X_0))}{\partial x_2} \frac{\partial \Phi_2(\tau_0,X_0)}{\partial x_2} \right) = \frac{\partial^2 \mathsf{z}_2^*(0,0)}{\partial \bar{\tau}^2} e_0' = 0.$

$$\frac{\partial^2 \mathsf{f}_2}{\partial \alpha^2}(\bar{\tau},\alpha) = \left[\frac{\partial^2 \mathsf{z}_2^*}{\partial \alpha^2} - \sum_{j=1}^{3} \sum_{i=1}^{3} \frac{\partial^2 \Theta_2(\Phi(\eta))}{\partial x_i \partial x_j} \frac{\partial}{\partial \alpha} \Phi_i(\eta) \frac{\partial}{\partial \alpha} \Phi_j(\eta) - \sum_{i=1}^{3} \frac{\partial \Theta_2(\Phi(\eta))}{\partial x_i} \frac{\partial^2}{\partial \alpha^2} \Phi_i(\eta) \right](\bar{\tau},\alpha),$$

where $\frac{\partial^2}{\partial \alpha^2} \Phi_i(\eta)(\bar{\tau},\alpha) = \left[\sum_{j=1}^{3} \sum_{k=1}^{3} \frac{\partial^2 \Phi_i(\eta)}{\partial x_j \partial x_k} \left(y_j + \frac{\partial \mathsf{z}_j^*}{\partial \alpha} \right) \left(y_k + \frac{\partial \mathsf{z}_k^*}{\partial \alpha} \right) + \sum_{j=1}^{3} \frac{\partial \Phi_i(\eta)}{\partial x_j} \frac{\partial^2 \mathsf{z}_j^*}{\partial \alpha^2} \right](\bar{\tau},\alpha).$

We obtain $\frac{\partial^2 \mathsf{f}_2}{\partial \alpha^2}(0,0) = \frac{\partial^2 \mathsf{z}_2^*(0,0)}{\partial \alpha^2} \left(1 - \frac{\partial \Theta_2(\Phi(\tau_0,X_0))}{\partial x_2} \frac{\partial \Phi_2(\tau_0,X_0)}{\partial x_2} \right) = \frac{\partial^2 \mathsf{z}_2^*(0,0)}{\partial \alpha^2} e_0' = 0.$

$$\frac{\partial^2 \mathsf{f}_2}{\partial\bar\tau\partial\alpha}(\bar\tau,\alpha) = \Bigg[\frac{\partial^2 \mathsf{z}_2^*}{\partial\bar\tau\partial\alpha} - \sum_{j=1}^{3}\sum_{i=1}^{3}\frac{\partial^2\Theta_2(\Phi(\eta))}{\partial x_i\partial x_j}\frac{\partial}{\partial\bar\tau}\Phi_i(\eta)\frac{\partial}{\partial\bar\tau}\Phi_j(\eta)) - \sum_{i=1}^{3}\frac{\partial\Theta_2(\Phi(\eta))}{\partial x_i}\frac{\partial^2}{\partial\bar\tau\partial\alpha}\Phi_i(\eta)\Bigg](\bar\tau,\alpha),$$

where $\frac{\partial^2}{\partial\bar\tau\partial\alpha}\Phi_i(\bar\tau,\alpha) = \Bigg[\sum_{j=1}^{3}\frac{\partial^2\Phi_i(\eta)}{\partial x_j\partial\bar\tau}\left(y_j + \frac{\partial \mathsf{z}_j^*}{\partial\alpha}\right) + \sum_{j=1}^{3}\sum_{k=1}^{3}\frac{\partial^2\Phi_i(\eta)}{\partial x_k\partial x_j}\frac{\partial \mathsf{z}_j^*}{\partial\bar\tau}\left(y_k + \frac{\partial \mathsf{z}_k^*}{\partial\alpha}\right) + \sum_{j=1}^{3}\frac{\partial\Phi_i(\eta)}{\partial x_j}\frac{\partial^2 \mathsf{z}_j^*}{\partial\bar\tau\partial\alpha}\Bigg](\bar\tau,\alpha).$

We obtain $\frac{\partial^2 \mathsf{f}_2}{\partial\bar\tau\partial\alpha}(0,0) = \frac{\partial^2 \mathsf{z}_2^*(0,0)}{\partial\bar\tau\partial\alpha}\left(1 - \frac{\partial\Theta_2(\Phi(\tau_0,X_0))}{\partial x_2}\frac{\partial\Phi_2(\tau_0,X_0)}{\partial x_2}\right) = \frac{\partial^2 \mathsf{z}_2^*(0,0)}{\partial\bar\tau\partial\alpha}e_0' = 0.$

5.4. **Third partial derivatives of $\mathbf{f}_2$.**

Let $\mathcal{A}_2 = \frac{\partial^3 \mathsf{f}_2}{\partial\bar\tau^3}(0,0)$, $\mathcal{B}_2 = \frac{\partial^3 \mathsf{f}_2}{\partial\bar\tau^2\partial\alpha}(0,0)$, $\mathcal{C}_2 = \frac{\partial^3 \mathsf{f}_2}{\partial\alpha^3}(0,0)$ and $\mathcal{D}_2 = \frac{\partial^3 \mathsf{f}_2}{\partial\alpha^2\partial\bar\tau}(0,0)$.

Calculation of $\mathcal{A}_2$.

$$\frac{\partial^3 \mathsf{f}_2}{\partial\bar\tau^3}(\bar\tau,\alpha) = \Bigg[\frac{\partial^3 \mathsf{z}_2^*}{\partial\bar\tau^3} - \sum_{k=1}^{3}\sum_{j=1}^{3}\sum_{i=1}^{3}\frac{\partial^3\Theta_2(\Phi(\eta))}{\partial x_i\partial x_j\partial x_k}\frac{\partial}{\partial\bar\tau}\Phi_i(\eta)\frac{\partial}{\partial\bar\tau}\Phi_j(\eta)\frac{\partial}{\partial\bar\tau}\Phi_k(\eta) - 3\sum_{j=1}^{3}\sum_{i=1}^{3}\frac{\partial^2\Theta_2(\Phi(\eta))}{\partial x_i\partial x_j}\frac{\partial^2}{\partial\bar\tau^2}\Phi_j(\eta)\frac{\partial}{\partial\bar\tau}\Phi_i(\eta) - \sum_{i=1}^{3}\frac{\partial\Theta_2(\Phi(\eta))}{\partial x_i}\frac{\partial^3}{\partial\bar\tau^3}\Phi_i(\eta)\Bigg](\bar\tau,\alpha),$$

where

$$\frac{\partial}{\partial\bar\tau^3}\Phi_i(\eta)(\bar\tau,\alpha) = \Bigg[\frac{\partial^3\Phi_i(\eta)}{\partial\bar\tau^3} + 3\sum_{j=1}^{3}\frac{\partial^3\Phi_i(\eta)}{\partial\bar\tau^2\partial x_j}\frac{\partial \mathsf{z}_j^*}{\partial\bar\tau} + 3\sum_{j=1}^{3}\sum_{k=1}^{3}\frac{\partial^3\Phi_i(\eta)}{\partial\bar\tau\partial x_j\partial x_k}\frac{\partial \mathsf{z}_j^*}{\partial\bar\tau}\frac{\partial \mathsf{z}_k^*}{\partial\bar\tau} + 3\sum_{j=1}^{3}\frac{\partial^2\Phi_i(\eta)}{\partial\bar\tau\partial x_j}\frac{\partial^2 \mathsf{z}_j^*}{\partial\bar\tau^2} + \sum_{j=1}^{3}\sum_{k=1}^{3}\sum_{l=1}^{3}\frac{\partial^3\Phi_i(\eta)}{\partial x_j\partial x_k\partial x_l}\frac{\partial \mathsf{z}_j^*}{\partial\bar\tau}\frac{\partial \mathsf{z}_k^*}{\partial\bar\tau}\frac{\partial \mathsf{z}_l^*}{\partial\bar\tau} + 3\sum_{j=1}^{3}\sum_{k=1}^{3}\frac{\partial^2\Phi_i(\eta)}{\partial x_j\partial x_k}\frac{\partial^2 \mathsf{z}_j^*}{\partial\bar\tau^2}\frac{\partial \mathsf{z}_k^*}{\partial\bar\tau} + \sum_{j=1}^{3}\frac{\partial\Phi_i(\eta)}{\partial x_j}\frac{\partial^3 \mathsf{z}_j^*}{\partial\bar\tau^3}\Bigg](\bar\tau,\alpha).$$

We obtain $\mathcal{A}_2 = \frac{\partial^3 \mathsf{z}_2^*(0,0)}{\partial\bar\tau^3}\left(1 - \frac{\partial\Theta_2(\Phi(\tau_0,X_0))}{\partial x_2}\frac{\partial\Phi_2(\tau_0,X_0)}{\partial x_2}\right) = \frac{\partial^3 \mathsf{z}_2^*(0,0)}{\partial\bar\tau^3}e_0' = 0.$

Calculation of $\mathcal{B}_2$.

$$\frac{\partial^3 \mathsf{f}_2}{\partial\bar\tau^2\partial\alpha}(\bar\tau,\alpha) = \Bigg[\frac{\partial^3 \mathsf{z}_2^*}{\partial\bar\tau^2\partial\alpha} - \sum_{k=1}^{3}\sum_{j=1}^{3}\sum_{i=1}^{3}\frac{\partial^3\Theta_2(\Phi(\eta))}{\partial x_i\partial x_j\partial x_k}\frac{\partial}{\partial\bar\tau}\Phi_i(\eta)\frac{\partial}{\partial\bar\tau}\Phi_j(\eta)\frac{\partial}{\partial\alpha}\Phi_k(\eta) - \sum_{i=1}^{3}\frac{\partial\Theta_2(\Phi(\eta))}{\partial x_i}\frac{\partial^3}{\partial\bar\tau^2\partial\alpha}\Phi_i(\eta) - 2\sum_{j=1}^{3}\sum_{i=1}^{3}\frac{\partial^2\Theta_2(\Phi(\eta))}{\partial x_i\partial x_j}\frac{\partial^2}{\partial\bar\tau\partial\alpha}\Phi_i(\eta)\frac{\partial}{\bar\tau}\Phi_j(\eta) - \sum_{j=1}^{3}\sum_{i=1}^{3}\frac{\partial^2\Theta_2(\Phi(\eta))}{\partial x_i\partial x_j}\frac{\partial^2}{\partial\bar\tau^2}\Phi_i(\eta)\frac{\partial}{\partial\alpha}\Phi_j(\eta)\Bigg](\bar\tau,\alpha),$$

where

$$\frac{\partial^3}{\partial\bar\tau^2\partial\alpha}\Phi_i(\eta)(\bar\tau,\alpha) = \Bigg[\sum_{j=1}^{3}\frac{\partial^3\Phi_i(\eta)}{\partial x_j\partial\bar\tau^2}\left(y_j + \frac{\partial \mathsf{z}_j^*}{\partial\alpha}\right) + 2\sum_{j=1}^{3}\sum_{k=1}^{3}\frac{\partial^3\Phi_i(\eta)}{\partial\bar\tau\partial x_j\partial x_k}\left(y_k + \frac{\partial \mathsf{z}_k^*}{\partial\alpha}\right)\frac{\partial \mathsf{z}_j^*}{\partial\bar\tau}$$

$$+2\sum_{j=1}^{3}\frac{\partial^2\Phi_i(\eta)}{\partial\bar{\tau}\partial x_j}\frac{\partial^2 \mathsf{z}_j^*}{\partial\bar{\tau}\partial\alpha}+\sum_{j=1}^{3}\sum_{k=1}^{3}\sum_{l=1}^{3}\frac{\partial^3\Phi_i(\eta)}{\partial x_j\partial x_k\partial x_l}\frac{\partial \mathsf{z}_j^*}{\partial\bar{\tau}}\frac{\partial \mathsf{z}_k^*}{\partial\bar{\tau}}\left(y_l+\frac{\partial \mathsf{z}_l^*}{\partial\alpha}\right)+2\sum_{j=1}^{3}\sum_{k=1}^{3}\frac{\partial^2\Phi_i(\eta)}{\partial x_j\partial x_k}\frac{\partial^2 \mathsf{z}_j^*}{\partial\bar{\tau}\partial\alpha}\frac{\partial \mathsf{z}_k^*}{\partial\bar{\tau}}$$
$$\left.+\sum_{j=1}^{3}\sum_{k=1}^{3}\frac{\partial^2\Phi_i(\eta)}{\partial x_j\partial x_k}\left(y_k+\frac{\partial \mathsf{z}_k^*}{\partial\alpha}\right)\frac{\partial^2 \mathsf{z}_j^*}{\partial\bar{\tau}^2}+\sum_{j=1}^{3}\frac{\partial\Phi_i(\eta)}{\partial x_j}\frac{\partial^3 \mathsf{z}_j^*}{\partial\bar{\tau}^2\partial\alpha}\right](\bar{\tau},\alpha).$$

We obtain

$$\mathcal{B}_2=-2\frac{\partial^2\Theta_2(\Phi(\tau_0,X_0))}{\partial x_1\partial x_2}\frac{\partial\Phi_2(\tau_0,X_0)}{\partial x_2}\left(\frac{\partial\Phi_1(\tau_0,X_0)}{\partial\bar{\tau}}+\frac{\partial\Phi_1(\tau_0,X_0)}{\partial x_1}\frac{\partial \mathsf{z}_1^*(0,0)}{\partial\bar{\tau}}\right)\frac{\partial^2 \mathsf{z}_2^*(0,0)}{\partial\bar{\tau}\partial\alpha}$$
$$-2\frac{\partial\Theta_2(\Phi(\tau_0,X_0))}{\partial x_2}\left(\frac{\partial^2\Phi_2(\tau_0,X_0)}{\partial\bar{\tau}\partial x_2}+\frac{\partial^2\Phi_2(\tau_0,X_0)}{\partial x_1\partial x_2}\frac{\partial \mathsf{z}_1^*(0,0)}{\partial\bar{\tau}}\right)\frac{\partial^2 \mathsf{z}_2^*(0,0)}{\partial\bar{\tau}\partial\alpha}.$$

Calculation of $\mathcal{C}_2$.

$$\frac{\partial^3\mathsf{f}_2}{\partial\alpha^3}(\bar{\tau},\alpha)=\left[\frac{\partial^3 \mathsf{z}_2^*}{\partial\alpha^3}-\sum_{k=1}^{3}\sum_{j=1}^{3}\sum_{i=1}^{3}\frac{\partial^3\Theta_2(\Phi(\eta))}{\partial x_i\partial x_j\partial x_k}\frac{\partial}{\partial\alpha}\Phi_i(\eta)\frac{\partial}{\partial\alpha}\Phi_j(\eta)\frac{\partial}{\partial\alpha}\Phi_k(\eta)\right.$$
$$\left.-3\sum_{j=1}^{3}\sum_{i=1}^{3}\frac{\partial^2\Theta_2(\Phi(\eta))}{\partial x_i\partial x_j}\frac{\partial^2}{\partial\alpha^2}\Phi_j(\eta)\frac{\partial}{\partial\alpha}\Phi_i(\eta)-\sum_{i=1}^{3}\frac{\partial\Theta_2(\Phi(\eta))}{\partial x_i}\frac{\partial^3}{\partial\alpha^3}\Phi_i(\eta)\right](\bar{\tau},\alpha),$$

where

$$\frac{\partial^3}{\partial\alpha^3}\Phi_i(\eta)(\bar{\tau},\alpha)=\left[\sum_{j=1}^{3}\sum_{k=1}^{3}\sum_{l=1}^{3}\frac{\partial^3\Phi_i(\eta)}{\partial x_j\partial x_k\partial x_l}\left(y_j+\frac{\partial \mathsf{z}_j^*}{\partial\alpha}\right)\left(y_k+\frac{\partial \mathsf{z}_k^*}{\partial\alpha}\right)\left(y_l+\frac{\partial \mathsf{z}_l^*}{\partial\alpha}\right)\right.$$
$$\left.+3\sum_{j=1}^{3}\sum_{k=1}^{3}\frac{\partial^2\Phi_i(\eta)}{\partial x_j\partial x_k}\frac{\partial^2 \mathsf{z}_j^*}{\partial\alpha^2}\left(y_k+\frac{\partial \mathsf{z}_k^*}{\partial\alpha}\right)+\sum_{j=1}^{3}\frac{\partial\Phi_i(\eta)}{\partial x_j}\frac{\partial^3 \mathsf{z}_j^*}{\partial\alpha^3}\right](\bar{\tau},\alpha).$$

We obtain

$$\mathcal{C}_2=-3\frac{\partial^2\Theta_2(\Phi(\tau_0,X_0))}{\partial x_1\partial x_2}\frac{\partial\Phi_2(\tau_0,X_0)}{\partial x_2}\left(\frac{\partial\Phi_1(\tau_0,X_0)}{\partial x_1}y_1+\frac{\partial\Phi_1(\tau_0,X_0)}{\partial x_3}\right)\frac{\partial^2 \mathsf{z}_2^*(0,0)}{\partial\alpha^2}$$
$$-3\frac{\partial^2\Theta_2(\Phi(\tau_0,X_0))}{\partial x_3\partial x_2}\frac{\partial\Phi_2(\tau_0,X_0)}{\partial x_2}\frac{\partial\Phi_3(\tau_0,X_0)}{\partial x_3}\frac{\partial^2 \mathsf{z}_2^*(0,0)}{\partial\alpha^2}$$
$$-3\frac{\partial\Theta_2(\Phi(\tau_0,X_0))}{\partial x_2}\left(\frac{\partial^2\Phi_2(\tau_0,X_0)}{\partial x_1\partial x_2}y_1+\frac{\partial^2\Phi_2(\tau_0,X_0)}{\partial x_3\partial x_2}\right)\frac{\partial^2 \mathsf{z}_2^*(0,0)}{\partial\alpha^2}.$$

Calculation of $\mathcal{D}_2$.

$$\frac{\partial^3\mathsf{f}_2}{\partial\alpha^2\partial\bar{\tau}}(\bar{\tau},\alpha)=\left[\frac{\partial^3 \mathsf{z}_2^*}{\partial\alpha^2\partial\bar{\tau}}-\sum_{k=1}^{3}\sum_{j=1}^{3}\sum_{i=1}^{3}\frac{\partial^3\Theta_2(\Phi(\eta))}{\partial x_i\partial x_j\partial x_k}\frac{\partial}{\partial\alpha}\Phi_i(\eta)\frac{\partial}{\partial\alpha}\Phi_j(\eta)\frac{\partial}{\partial\bar{\tau}}\Phi_k(\eta)\right.$$
$$-\sum_{i=1}^{3}\frac{\partial\Theta_2(\Phi(\eta))}{\partial x_i}\frac{\partial^3}{\partial\bar{\tau}\partial\alpha^2}\Phi_i(\eta)-2\sum_{j=1}^{3}\sum_{i=1}^{3}\frac{\partial^2\Theta_2(\Phi(\eta))}{\partial x_i\partial x_j}\frac{\partial^2}{\partial\bar{\tau}\partial\alpha}\Phi_i(\eta)\frac{\partial}{\partial\alpha}\Phi_j(\eta)$$
$$\left.-\sum_{j=1}^{3}\sum_{i=1}^{3}\frac{\partial^2\Theta_2(\Phi(\eta))}{\partial x_i\partial x_j}\frac{\partial^2}{\partial\alpha^2}\Phi_i(\eta)\frac{\partial}{\partial\bar{\tau}}\Phi_j(\eta)\right](\bar{\tau},\alpha),$$

where

$$\frac{\partial^3}{\partial\bar{\tau}\partial\alpha^2}\Phi_i(\eta)(\bar{\tau},\alpha)=\left[\sum_{j=1}^{3}\sum_{k=1}^{3}\frac{\partial^3\Phi_i(\eta)}{\partial\bar{\tau}\partial x_j\partial x_k}\left(y_k+\frac{\partial \mathsf{z}_k^*}{\partial\alpha}\right)\left(y_j+\frac{\partial \mathsf{z}_j^*}{\partial\alpha}\right)+\sum_{j=1}^{3}\frac{\partial^2\Phi_i(\eta)}{\partial\bar{\tau}\partial x_j}\frac{\partial^2 \mathsf{z}_j^*}{\partial\alpha^2}\right.$$
$$+\sum_{j=1}^{3}\sum_{k=1}^{3}\sum_{l=1}^{3}\frac{\partial^3\Phi_i(\eta)}{\partial x_j\partial x_k\partial x_l}\left(y_j+\frac{\partial \mathsf{z}_j^*}{\partial\alpha}\right)\frac{\partial \mathsf{z}_k^*}{\partial\bar{\tau}}\left(y_l+\frac{\partial \mathsf{z}_l^*}{\partial\alpha}\right)+\sum_{j=1}^{3}\frac{\partial\Phi_i(\eta)}{\partial x_j}\frac{\partial^3 \mathsf{z}_j^*}{\partial\bar{\tau}\partial\alpha^2}$$
$$\left.+2\sum_{j=1}^{3}\sum_{k=1}^{3}\frac{\partial^2\Phi_i(\eta)}{\partial x_j\partial x_k}\frac{\partial^2 z_k^*}{\partial\bar{\tau}\partial\alpha}\left(y_j+\frac{\partial \mathsf{z}_j^*}{\partial\alpha}\right)+\sum_{j=1}^{3}\sum_{k=1}^{3}\frac{\partial^2\Phi_i(\eta)}{\partial x_j\partial x_k}\frac{\partial \mathsf{z}_k^*}{\partial\bar{\tau}}\frac{\partial^2 \mathsf{z}_j^*}{\partial\alpha^2}\right](\bar{\tau},\alpha).$$

We obtain

$$\begin{aligned}\mathcal{D}_2 = &-2\frac{\partial\Phi_2(\tau_0,X_0)}{\partial x_2}\frac{\partial^2 \mathsf{z}_2^*(0,0)}{\partial\bar\tau\partial\alpha}\frac{\partial^2\Theta_2(\Phi(\tau_0,X_0))}{\partial x_1\partial x_2}\left(\frac{\partial\Phi_1(\tau_0,X_0)}{\partial x_1}y_1+\frac{\partial\Phi_1(\tau_0,X_0)}{\partial x_3}\right)\\
&-2\frac{\partial\Phi_2(\tau_0,X_0)}{\partial x_2}\frac{\partial^2 \mathsf{z}_2^*(0,0)}{\partial\bar\tau\partial\alpha}\frac{\partial^2\Theta_2(\Phi(\tau_0,X_0))}{\partial x_3\partial x_2}\frac{\partial\Phi_3(\tau_0,X_0)}{\partial x_3}\\
&-2\frac{\partial\Theta_2(\Phi(\tau_0,X_0))}{\partial x_2}\left(\frac{\partial^2\Phi_2(\tau_0,X_0)}{\partial x_1\partial x_2}y_1+\frac{\partial^2\Phi_2(\tau_0,X_0)}{\partial x_3\partial x_2}\right)\frac{\partial^2 \mathsf{z}_2^*(0,0)}{\partial\bar\tau\partial\alpha}\\
&-\frac{\partial^2\Theta_2(\Phi(\tau_0,X_0))}{\partial x_1\partial x_2}\frac{\partial\Phi_2(\tau_0,X_0)}{\partial x_2}\left(\frac{\partial\Phi_1(\tau_0,X_0)}{\partial\bar\tau}+\frac{\partial\Phi_1(\tau_0,X_0)}{\partial x_1}\frac{\partial \mathsf{z}_1^*(0,0)}{\partial\bar\tau}\right)\frac{\partial^2 \mathsf{z}_2^*(0,0)}{\partial\alpha^2}\\
&-\frac{\partial\Theta_2(\Phi(\tau_0,X_0))}{\partial x_2}\left(\frac{\partial^2\Phi_2(\tau_0,X_0)}{\partial\bar\tau\partial x_2}+\frac{\partial^2\Phi_2(\tau_0,X_0)}{\partial x_1\partial x_2}\frac{\partial \mathsf{z}_1^*(0,0)}{\partial\bar\tau}\right)\frac{\partial^2 \mathsf{z}_2^*(0,0)}{\partial\alpha^2}.\end{aligned}$$

6. Appendix C: Case $h_0' = 0$

Let $\eta_0(\bar\tau)=\tau_0+\bar\tau$, $\eta_1(\bar\tau,\alpha,\beta)=x_0-\frac{b_0'}{a_0'}\alpha-\frac{c_0'}{a_0'}\beta+z_1^*(\bar\tau,\alpha,\beta)$, $\eta_2(\bar\tau,\alpha,\beta)=\alpha$, $\eta_3(\bar\tau,\alpha,\beta)=\beta$, $\eta(\bar\tau,\alpha,\beta)=(\eta_0,\eta_1,\eta_2,\eta_3)(\bar\tau,\alpha,\beta)$, $Y_0=(y_1,y_2,y_3)$, $y_1=-\frac{b_0'}{a_0'}$, $y_2=1$, $y_3=0$, $Y_1=(y_1',y_2',y_3')$, $y_1'=-\frac{c_0'}{a_0'}$, $y_2'=0$, $y_3'=1$.
For $i=2,3$ let $A_i=\frac{\partial^2 f_i}{\partial\bar\tau^2}(0,0,0)$, $B_i=\frac{\partial^2 f_i}{\partial\alpha^2}(0,0,0)$, $C_i=\frac{\partial^2 f_i}{\partial\beta^2}(0,0,0)$, $D_i=\frac{\partial^2 f_i}{\partial\bar\tau\partial\alpha}(0,0,0)$, $E_i=\frac{\partial^2 f_i}{\partial\bar\tau\partial\beta}(0,0,0)$ and $F_i=\frac{\partial^2 f_i}{\partial\alpha\partial\beta}(0,0,0)$.

6.1. First partial derivatives of $Z^*=(z_1^*,0,0)$.

From the first partial derivatives of equations (2.7), we obtain
$\frac{\partial z_1^*}{\partial\bar\tau}(0,0,0)=a_0'^{-1}\frac{\partial\Theta_1(\Phi(\tau_0,X_0))}{\partial x_1}\frac{\partial\Phi_1(\tau_0,X_0)}{\partial\bar\tau}$, $\frac{\partial z_1^*}{\partial\alpha}(0,0,0)=0$, and $\frac{\partial z_1^*}{\partial\beta}(0,0,0)=0$.

6.2. First partial derivatives of f_2.

$$\frac{\partial f_2}{\partial\bar\tau}(\bar\tau,\alpha,\beta)=\frac{\partial}{\partial\bar\tau}\left(\eta_2-\Theta_2\circ\Phi(\eta)\right)(\bar\tau,\alpha,\beta)=\left[-\sum_{i=1}^{3}\frac{\partial\Theta_2(\Phi(\eta))}{\partial x_i}\frac{\partial}{\partial\bar\tau}\Phi_i(\eta)\right](\bar\tau,\alpha,\beta).$$

Since $\frac{\partial\Theta_2(\Phi(\eta))}{\partial x_1}(0,0,0)=\frac{\partial\Theta_2(\Phi(\eta))}{\partial x_3}(0,0,0)=0$, $\frac{\partial\Phi_2(\eta)}{\partial x_1}(0,0,0)=\frac{\partial\Phi_2(\eta)}{\partial x_3}(0,0,0)=0$ and $\frac{\partial\Phi_2(\eta)}{\partial\bar\tau}(0,0,0)=0$, we obtain $\frac{\partial f_2}{\partial\bar\tau}(0,0,0)=0$.

$$\frac{\partial f_2}{\partial\alpha}(\bar\tau,\alpha,\beta)=\left[1-\sum_{i=1}^{3}\frac{\partial\Theta_2(\Phi(\eta))}{\partial x_i}\frac{\partial}{\partial\alpha}\Phi_i(\eta)\right](\bar\tau,\alpha,\beta).$$

We obtain $\frac{\partial f_2}{\partial\alpha}(0,0,0)=1-\frac{\partial\Theta_2(\Phi(\tau_0,X_0))}{\partial x_2}\frac{\partial\Phi_2(\tau_0,X_0)}{\partial x_2}=e_0'=0$.

$$\frac{\partial f_2}{\partial\beta}(\bar\tau,\alpha,\beta)=\left[-\sum_{i=1}^{3}\frac{\partial\Theta_2(\Phi(\eta))}{\partial x_i}\frac{\partial}{\partial\beta}\Phi_i(\eta)\right](\bar\tau,\alpha,\beta),$$

where $\frac{\partial}{\partial\beta}\Phi_i(\eta)(\bar\tau,\alpha,\beta)=\left[\sum_{j=1}^{3}\frac{\partial\Phi_i(\eta)}{\partial x_j}\left(y_j'+\frac{\partial z_j^*}{\partial\beta}\right)\right](\bar\tau,\alpha,\beta)$.

We obtain $\frac{\partial f_2}{\partial\beta}(0,0,0)=0$.

6.3. First partial derivatives of f_3.

$$\frac{\partial f_3}{\partial\bar\tau}(\bar\tau,\alpha,\beta)=\left[\frac{\partial}{\partial\bar\tau}\left(\eta_3-\Theta_3\circ\Phi(\eta)\right)=-\sum_{i=1}^{3}\frac{\partial\Theta_3(\Phi(\eta))}{\partial x_i}\frac{\partial}{\partial\bar\tau}\Phi_i(\eta)\right](\bar\tau,\alpha,\beta).$$

Since $\frac{\partial\Theta_3(\Phi(\eta))}{\partial x_1}(0,0,0)=0$, $\frac{\partial\Phi_2(\eta)}{\partial x_1}(0,0,0)=\frac{\partial\Phi_3(\eta)}{\partial x_1}(0,0,0)=0$, and $\frac{\partial\Phi_2(\eta)}{\partial\bar\tau}(0,0,0)=\frac{\partial\Phi_3(\eta)}{\partial\bar\tau}(0,0,0)=0$, we obtain $\frac{\partial f_3}{\partial\bar\tau}(0,0,0)=0$.

$$\frac{\partial f_3}{\partial\alpha}(\bar\tau,\alpha,\beta)=\left[-\sum_{i=1}^{3}\frac{\partial\Theta_3(\Phi(\eta))}{\partial x_i}\frac{\partial}{\partial\alpha}\Phi_i(\eta)\right](\bar\tau,\alpha,\beta).$$

We obtain $\frac{\partial f_3}{\partial \alpha}(0,0,0) = h_0' = 0$.

$\frac{\partial f_3}{\partial \beta}(\bar{\tau},\alpha,\beta) = \left[1 - \sum_{i=1}^{3} \frac{\partial \Theta_3(\Phi(\eta))}{\partial x_i} \frac{\partial}{\partial \beta}\Phi_i(\eta)\right](\bar{\tau},\alpha,\beta)$.

We obtain $\frac{\partial f_3}{\partial \beta}(0,0,0) = 1 - \frac{\partial \Theta_3(\Phi(\tau_0,X_0))}{\partial x_3}\frac{\partial \Phi_3(\tau_0,X_0)}{\partial x_3} = i_0' = 0$.

6.4. **Second partial derivatives of f_2.**

Calculation of A_2.

$$\frac{\partial^2 f_2}{\partial \bar{\tau}^2}(\bar{\tau},\alpha,\beta) = -\sum_{i=1}^{3}\left[\sum_{j=1}^{3}\frac{\partial^2\Theta_2(\Phi(\eta))}{\partial x_i\partial x_j}\frac{\partial}{\partial\bar{\tau}}\Phi_i(\eta)\frac{\partial}{\partial\bar{\tau}}\Phi_j(\eta) + \frac{\partial\Theta_2(\Phi(\eta))}{\partial x_i}\frac{\partial^2}{\partial\bar{\tau}^2}\Phi_i(\eta)\right](\bar{\tau},\alpha,\beta),$$

where

$$\frac{\partial^2}{\partial\bar{\tau}^2}\Phi_i(\eta)(\bar{\tau},\alpha,\beta) = \left[\frac{\partial^2\Phi_i(\eta)}{\partial\bar{\tau}^2} + 2\frac{\partial^2\Phi_i(\eta)}{\partial\bar{\tau}\partial x_1}\frac{\partial z_1^*}{\partial\bar{\tau}} + \frac{\partial\Phi_i(\eta)}{\partial x_1}\frac{\partial^2 z_1^*}{\partial\bar{\tau}^2} + \frac{\partial^2\Phi_i(\eta)}{\partial x_1^2}\left(\frac{\partial z_1^*}{\partial\bar{\tau}}\right)^2\right](\bar{\tau},\alpha,\beta).$$

We obtain $A_2 = 0$.

Calculation of B_2.

$$\frac{\partial^2 f_2(\eta)}{\partial \alpha^2}(\bar{\tau},\alpha,\beta) = -\sum_{i=1}^{3}\left[\sum_{j=1}^{3}\frac{\partial^2\Theta_2(\Phi(\eta))}{\partial x_i\partial x_j}\frac{\partial}{\partial\alpha}\Phi_i(\eta)\frac{\partial}{\partial\alpha}\Phi_j(\eta) + \frac{\partial\Theta_2(\Phi(\eta))}{\partial x_i}\frac{\partial^2}{\partial\alpha^2}\Phi_i(\eta)\right](\bar{\tau},\alpha,\beta),$$

where

$$\begin{aligned}\frac{\partial^2}{\partial\alpha^2}\Phi_i(\eta)(\bar{\tau},\alpha,\beta) = \Bigg[&\frac{\partial^2\Phi_i(\eta)}{\partial x_1^2}\left(\frac{\partial z_1^*}{\partial\alpha} - \frac{b_0'}{a_0'}\right)^2 + 2\frac{\partial^2\Phi_i(\eta)}{\partial x_1\partial x_2}\left(\frac{\partial z_1^*}{\partial\alpha} - \frac{b_0'}{a_0'}\right)\\ &+\frac{\partial\Phi_i(\eta)}{\partial x_1}\frac{\partial^2 z_1^*}{\partial\alpha^2} + \frac{\partial^2\Phi_i(\eta)}{\partial x_2^2}\Bigg](\bar{\tau},\alpha,\beta).\end{aligned}$$

We obtain

$$\begin{aligned}B_2 = &-2\frac{\partial^2\Theta_2(\Phi(\tau_0,X_0))}{\partial x_1\partial x_2}\frac{\partial\Phi_2(\tau_0,X_0)}{\partial x_2}\left(\frac{\partial\Phi_1(\tau_0,X_0)}{\partial x_1}(-\frac{b_0'}{a_0'}) + \frac{\partial\Phi_1(\tau_0,X_0)}{\partial x_2}\right)\\ &- \frac{\partial^2\Theta_2(\Phi(\tau_0,X_0))}{\partial x_2^2}\left(\frac{\partial\Phi_2(\tau_0,X_0)}{\partial x_2}\right)^2 - 2\frac{\partial^2\Theta_2(\Phi(\tau_0,X_0))}{\partial x_3\partial x_2}\frac{\partial\Phi_3(\tau_0,X_0)}{\partial x_2}\frac{\partial\Phi_2(\tau_0,X_0)}{\partial x_2}\\ &- \frac{\partial\Theta_2(\Phi(\tau_0,X_0))}{\partial x_2}\left(2\frac{\partial^2\Phi_2(\tau_0,X_0)}{\partial x_1\partial x_2}(-\frac{b_0'}{a_0'}) + \frac{\partial^2\Phi_2(\tau_0,X_0)}{\partial x_2^2}\right).\end{aligned}$$

Calculation of C_2.

$$\frac{\partial^2 f_2}{\partial \beta^2}(\bar{\tau},\alpha,\beta) = -\sum_{i=1}^{3}\left[\sum_{j=1}^{3}\frac{\partial^2\Theta_2(\Phi(\eta))}{\partial x_i\partial x_j}\frac{\partial}{\partial\beta}\Phi_i(\eta)\frac{\partial}{\partial\beta}\Phi_j(\eta) + \frac{\partial\Theta_2(\eta))}{\partial x_i}\frac{\partial^2}{\partial\beta^2}\Phi_i(\eta)\right](\bar{\tau},\alpha,\beta),$$

where

$$\begin{aligned}\frac{\partial^2}{\partial\beta^2}\Phi_i(\eta)(\bar{\tau},\alpha,\beta) = \Bigg[&\frac{\partial^2\Phi_i(\eta)}{\partial x_1^2}\left(\frac{\partial z_1^*}{\partial\beta} - \frac{c_0'}{a_0'}\right)^2 + 2\frac{\partial^2\Phi_i(\eta)}{\partial x_1\partial x_3}\left(\frac{\partial z_1^*}{\partial\beta} - \frac{c_0'}{a_0'}\right)\\ &+\frac{\partial\Phi_i(\eta)}{\partial x_1}\frac{\partial^2 z_1^*}{\partial\beta^2} + \frac{\partial^2\Phi_i(\eta)}{\partial x_3^2}\Bigg](\bar{\tau},\alpha,\beta).\end{aligned}$$

We obtain $C_2 = 0$.

Calculation of D_2.

$$\frac{\partial^2 f_2}{\partial \bar{\tau}\partial\alpha}(\bar{\tau},\alpha,\beta) = -\sum_{i=1}^{3}\left[\sum_{j=1}^{3}\frac{\partial^2\Theta_2(\Phi(\eta))}{\partial x_i\partial x_j}\frac{\partial}{\partial\alpha}\Phi_j(\eta)\frac{\partial}{\partial\bar{\tau}}\Phi_i(\eta) + \frac{\partial\Theta_2(\Phi(\eta))}{\partial x_i}\frac{\partial^2}{\partial\bar{\tau}\partial\alpha}\Phi_i(\eta)\right](\bar{\tau},\alpha,\beta),$$

where

$$\begin{aligned}\frac{\partial^2}{\partial\bar{\tau}\partial\alpha}\Phi_i(\eta)(\bar{\tau},\alpha,\beta) = \Bigg[&\left(\frac{\partial z_1^*}{\partial\alpha} - \frac{b_0'}{a_0'}\right)\left(\frac{\partial^2\Phi_i(\eta)}{\partial\bar{\tau}\partial x_1} + \frac{\partial^2\Phi_i(\eta)}{\partial x_1^2}\frac{\partial z_1^*}{\partial\bar{\tau}}\right) + \frac{\partial\Phi_i(\eta)}{\partial x_1}\frac{\partial^2 z_1^*}{\partial\bar{\tau}\partial\alpha}\\ &+\frac{\partial^2\Phi_i(\eta)}{\partial\bar{\tau}\partial x_2} + \frac{\partial^2\Phi_i(\eta)}{\partial x_1\partial x_2}\frac{\partial z_1^*}{\partial\bar{\tau}}\Bigg](\bar{\tau},\alpha,\beta).\end{aligned}$$

We obtain

$$\begin{aligned}D_2 = &-\frac{\partial^2\Theta_2(\Phi(\tau_0,X_0))}{\partial x_1\partial x_2}\frac{\partial\Phi_2(\tau_0,X_0)}{\partial x_2}\left[\frac{\partial\Phi_1(\tau_0,X_0)}{\partial\bar{\tau}} + \frac{\partial\Phi_1(\tau_0,X_0)}{\partial x_1}\frac{\partial z_1^*(0,0,0)}{\partial\bar{\tau}}\right]\\ &- \frac{\partial\Theta_2(\Phi(\tau_0,X_0))}{\partial x_2}\left[\frac{\partial^2\Phi_2(\tau_0,X_0)}{\partial\bar{\tau}\partial x_2} + \frac{\partial^2\Phi_2(\tau_0,X_0)}{\partial x_1\partial x_2}\frac{\partial z_1^*(0,0,0)}{\partial\bar{\tau}}\right].\end{aligned}$$

Calculation of E_2.

$$\frac{\partial^2 f_2}{\partial\bar\tau\partial\beta}(\bar\tau,\alpha,\beta) = -\sum_{i=1}^{3}\left[\sum_{j=1}^{3}\frac{\partial^2\Theta_2(\Phi(\eta))}{\partial x_i\partial x_j}\frac{\partial}{\partial\beta}\Phi_j(\eta)\frac{\partial}{\partial\bar\tau}\Phi_i(\eta)+\frac{\partial\Theta_2(\Phi(\eta))}{\partial x_i}\frac{\partial^2}{\partial\bar\tau\partial\beta}\Phi_i(\eta)\right](\bar\tau,\alpha,\beta),$$

where

$$\frac{\partial^2}{\partial\bar\tau\partial\beta}\Phi_i(\eta)(\bar\tau,\alpha,\beta) = \Big[\left(\frac{\partial z_1^*}{\partial\beta}-\frac{c_0'}{a_0'}\right)\left(\frac{\partial^2\Phi_i(\eta)}{\partial\bar\tau\partial x_1}+\frac{\partial^2\Phi_i(\eta)}{\partial x_1^2}\frac{\partial z_1^*}{\partial\bar\tau}\right)+\frac{\partial\Phi_i(\eta)}{\partial x_1}\frac{\partial^2 z_1^*}{\partial\bar\tau\partial\beta}$$
$$+\frac{\partial^2\Phi_i(\eta)}{\partial\bar\tau\partial x_3}+\frac{\partial^2\Phi_i(\eta)}{\partial x_1\partial x_3}\frac{\partial z_1^*}{\partial\bar\tau}\Big](\bar\tau,\alpha,\beta).$$

We obtain $E_2 = 0$.

Calculation of F_2.

$$\frac{\partial^2 f_2}{\partial\alpha\partial\beta}(\bar\tau,\alpha,\beta) = -\sum_{i=1}^{3}\left[\sum_{j=1}^{3}\frac{\partial^2\Theta_2(\Phi(\eta))}{\partial x_i\partial x_j}\frac{\partial}{\partial\alpha}\Phi_i(\eta)\frac{\partial}{\partial\beta}\Phi_j(\eta)+\frac{\partial\Theta_2(\Phi(\eta))}{\partial x_i}\frac{\partial^2}{\partial\alpha\partial\beta}\Phi_i(\eta)\right](\bar\tau,\alpha,\beta),$$

where

$$\frac{\partial^2}{\partial\alpha\partial\beta}\Phi_i(\eta)(\bar\tau,\alpha,\beta) = \Big[\left(-\frac{c_0'}{a_0'}+\frac{\partial z_1^*}{\partial\beta}\right)\left(\frac{\partial^2\Phi_i(\eta)}{\partial x_1^2}\left(-\frac{b_0'}{a_0'}+\frac{\partial z_1^*}{\partial\alpha}\right)+\frac{\partial^2\Phi_i(\eta)}{\partial x_2\partial x_1}\right)$$
$$+\frac{\partial\Phi_i(\eta)}{\partial x_1}\frac{\partial^2 z_1^*}{\partial\alpha\partial\beta}+\frac{\partial^2\Phi_i(\eta)}{\partial x_1\partial x_3}\left(-\frac{b_0'}{a_0'}+\frac{\partial z_1^*}{\partial\alpha}\right)+\frac{\partial^2\Phi_i(\eta)}{\partial x_2\partial x_3}\Big](\bar\tau,\alpha,\beta).$$

We obtain

$$F_2 = -\frac{\partial^2\Theta_2(\Phi(\tau_0,X_0))}{\partial x_1\partial x_2}\frac{\partial\Phi_2(\tau_0,X_0)}{\partial x_2}\left(-\frac{c_0'}{a_0'}\frac{\partial\Phi_1(\tau_0,X_0)}{\partial x_1}+\frac{\partial\Phi_1(\tau_0,X_0)}{\partial x_3}\right)$$
$$-\frac{\partial\Theta_2(\Phi(\tau_0,X_0))}{\partial x_2}\left(-\frac{c_0'}{a_0'}\frac{\partial^2\Phi_2(\tau_0,X_0)}{\partial x_1\partial x_2}+\frac{\partial^2\Phi_2(\tau_0,X_0)}{\partial x_3\partial x_2}\right)-\frac{\partial^2\Theta_2(\Phi(\tau_0,X_0))}{\partial x_3\partial x_2}\frac{\partial\Phi_2(\tau_0,X_0)}{\partial x_2}\frac{\partial\Phi_3(\tau_0,X_0)}{\partial x_3}.$$

6.5. **Second partial derivatives of f_3.**

Calculation of A_3.

$$\frac{\partial^2 f_3}{\partial\bar\tau^2}(\bar\tau,\alpha,\beta) = -\sum_{i=1}^{3}\left[\sum_{j=1}^{3}\frac{\partial^2\Theta_3(\Phi(\eta))}{\partial x_i\partial x_j}\frac{\partial}{\partial\bar\tau}\Phi_i(\eta)\frac{\partial}{\partial\bar\tau}\Phi_j(\eta)+\frac{\partial\Theta_3(\Phi(\eta))}{\partial x_i}\frac{\partial^2}{\partial\bar\tau^2}\Phi_i(\eta)\right](\bar\tau,\alpha,\beta).$$

We obtain $A_3 = 0$.

Calculation of B_3.

$$\frac{\partial^2 f_3}{\partial\alpha^2}(\bar\tau,\alpha,\beta) = -\sum_{i=1}^{3}\left[\sum_{j=1}^{3}\frac{\partial^2\Theta_3(\Phi(\eta))}{\partial x_i\partial x_j}\frac{\partial}{\partial\alpha}\Phi_i(\eta)\frac{\partial}{\partial\alpha}\Phi_j(\eta)+\frac{\partial\Theta_3(\Phi(\eta))}{\partial x_i}\frac{\partial^2}{\partial\alpha^2}\Phi_i(\eta)\right](\bar\tau,\alpha,\beta).$$

We obtain

$$B_3 = -2\frac{\partial^2\Theta_3(\Phi(\tau_0,X_0))}{\partial x_2\partial x_1}\frac{\partial\Phi_2(\tau_0,X_0)}{\partial x_2}\left[\frac{\partial\Phi_1(\tau_0,X_0)}{\partial x_1}\left(-\frac{b_0'}{a_0'}+\frac{\partial z_1^*}{\partial\alpha}\right)+\frac{\partial\Phi_1(\tau_0,X_0)}{\partial x_2}\right]$$
$$-2\frac{\partial^2\Theta_3(\Phi(\tau_0,X_0))}{\partial x_3\partial x_1}\frac{\partial\Phi_3(\tau_0,X_0)}{\partial x_2}\left[\frac{\partial\Phi_1(\tau_0,X_0)}{\partial x_1}\left(-\frac{b_0'}{a_0'}+\frac{\partial z_1^*}{\partial\alpha}\right)+\frac{\partial\Phi_1(\tau_0,X_0)}{\partial x_2}\right]$$
$$-\frac{\partial^2\Theta_3(\Phi(\tau_0,X_0))}{\partial x_2^2}\left(\frac{\partial\Phi_2(\tau_0,X_0)}{\partial x_2}\right)^2-2\frac{\partial^2\Theta_3(\Phi(\tau_0,X_0))}{\partial x_3\partial x_2}\frac{\partial\Phi_3(\tau_0,X_0)}{\partial x_2}\frac{\partial\Phi_2(\tau_0,X_0)}{\partial x_2}$$
$$-\frac{\partial\Theta_3(\Phi(\tau_0,X_0))}{\partial x_2}\left[\frac{\partial^2\Phi_2(\tau_0,X_0)}{\partial x_2^2}-2\frac{\partial^2\Phi_2(\tau_0,X_0)}{\partial x_1\partial x_2}\frac{b_0'}{a_0'}\right]-\frac{\partial^2\Theta_3(\Phi(\tau_0,X_0))}{\partial x_3^2}\left(\frac{\partial\Phi_3(\tau_0,X_0)}{\partial x_2}\right)^2$$
$$-\frac{\partial\Theta_3(\Phi(\tau_0,X_0))}{\partial x_3}\left[\frac{\partial^2\Phi_3(\tau_0,X_0)}{\partial x_2^2}-2\frac{\partial^2\Phi_3(\tau_0,X_0)}{\partial x_1\partial x_2}\frac{b_0'}{a_0'}\right].$$

Calculation of C_3.

$$\frac{\partial^2 f_3}{\partial\beta^2}(\bar\tau,\alpha,\beta) = -\sum_{i=1}^{3}\left[\sum_{j=1}^{3}\frac{\partial^2\Theta_3(\Phi(\eta))}{\partial x_i\partial x_j}\frac{\partial}{\partial\beta}\Phi_i(\eta)\frac{\partial}{\partial\beta}\Phi_j(\eta)+\frac{\partial\Theta_3(\Phi(\eta))}{\partial x_i}\frac{\partial^2}{\partial\beta^2}\Phi_i(\eta)\right](\bar\tau,\alpha,\beta).$$

We obtain

$$C_3 = -2\frac{\partial^2\Theta_3(\Phi(\tau_0,X_0))}{\partial x_3\partial x_1}\frac{\partial\Phi_3(\tau_0,X_0)}{\partial x_3}\left[\frac{\partial\Phi_1(\tau_0,X_0)}{\partial x_1}\left(-\frac{c_0'}{a_0'}\right)+\frac{\partial\Phi_1(\tau_0,X_0)}{\partial x_3}\right]$$
$$-\frac{\partial^2\Theta_3(\Phi(\tau_0,X_0))}{\partial x_3^2}\left(\frac{\partial\Phi_3(\tau_0,X_0)}{\partial x_3}\right)^2-\frac{\partial\Theta_3(\Phi(\tau_0,X_0))}{\partial x_3}\left[\frac{\partial^2\Phi_3(\tau_0,X_0)}{\partial x_3^2}-2\frac{\partial^2\Phi_3(\tau_0,X_0)}{\partial x_1\partial x_3}\frac{c_0'}{a_0'}\right].$$

Calculation of D_3.

$$\frac{\partial^2 f_3}{\partial\bar{\tau}\partial\alpha}(\bar{\tau},\alpha,\beta) = -\sum_{i=1}^{3}\left[\sum_{j=1}^{3}\frac{\partial^2\Theta_3(\Phi(\eta))}{\partial x_i\partial x_j}\frac{\partial}{\partial\alpha}\Phi_j(\eta)\frac{\partial}{\partial\bar{\tau}}\Phi_i(\eta) + \frac{\partial\Theta_3(\Phi(\eta))}{\partial x_i}\frac{\partial^2}{\partial\bar{\tau}\alpha}\Phi_i(\eta)\right](\bar{\tau},\alpha,\beta).$$

We obtain

$$\begin{aligned}
D_3 = &-\frac{\partial^2\Theta_3(\Phi(\tau_0,X_0))}{\partial x_2\partial x_1}\frac{\partial\Phi_2(\tau_0,X_0)}{\partial x_2}\left(\frac{\partial\Phi_1(\tau_0,X_0)}{\partial\bar{\tau}} + \frac{\partial\Phi_1(\tau_0,X_0)}{\partial x_1}\frac{\partial z_1^*(0,0,0)}{\partial\bar{\tau}}\right)\\
&-\frac{\partial^2\Theta_3(\Phi(\tau_0,X_0))}{\partial x_1\partial x_3}\frac{\partial\Phi_3(\tau_0,X_0)}{\partial x_2}\left(\frac{\partial\Phi_1(\tau_0,X_0)}{\partial\bar{\tau}} + \frac{\partial\Phi_1(\tau_0,X_0)}{\partial x_1}\frac{\partial z_1^*(0,0,0)}{\partial\bar{\tau}}\right)\\
&-\frac{\partial\Theta_3(\Phi(\tau_0,X_0))}{\partial x_2}\left(\frac{\partial^2\Phi_2(\tau_0,X_0)}{\partial\bar{\tau}\partial x_2} + \frac{\partial^2\Phi_2(\tau_0,X_0)}{\partial x_1\partial x_2}\frac{\partial z_1^*(0,0,0)}{\partial\bar{\tau}}\right)\\
&-\frac{\partial\Theta_3(\Phi(\tau_0,X_0))}{\partial x_3}\left(\frac{\partial^2\Phi_3(\tau_0,X_0)}{\partial\bar{\tau}\partial x_2} + \frac{\partial^2\Phi_3(\tau_0,X_0)}{\partial x_1\partial x_2}\frac{\partial z_1^*(0,0,0)}{\partial\bar{\tau}}\right).
\end{aligned}$$

Calculation of E_3.

$$\frac{\partial^2 f_3}{\partial\bar{\tau}\partial\beta}(\bar{\tau},\alpha,\beta) = -\sum_{i=1}^{3}\left[\sum_{j=1}^{3}\frac{\partial^2\Theta_3(\Phi(\eta))}{\partial x_i\partial x_j}\frac{\partial}{\partial\beta}\Phi_j(\eta)\frac{\partial}{\partial\bar{\tau}}\Phi_i(\eta) + \frac{\partial\Theta_3(\Phi(\eta))}{\partial x_i}\frac{\partial^2}{\partial\bar{\tau}\partial\beta}\Phi_i(\eta)\right](\bar{\tau},\alpha,\beta).$$

We obtain

$$\begin{aligned}
E_3 = &-\frac{\partial^2\Theta_3(\Phi(\tau_0,X_0))}{\partial x_1\partial x_3}\frac{\partial\Phi_3(\tau_0,X_0)}{\partial x_3}\left(\frac{\partial\Phi_1(\tau_0,X_0)}{\partial\bar{\tau}} + \frac{\partial\Phi_1(\tau_0,X_0)}{\partial x_1}\frac{\partial z_1^*(0,0,0)}{\partial\bar{\tau}}\right)\\
&-\frac{\partial\Theta_3(\Phi(\tau_0,X_0))}{\partial x_3}\left(\frac{\partial^2\Phi_3(\tau_0,X_0)}{\partial\bar{\tau}\partial x_3} + \frac{\partial^2\Phi_3(\tau_0,X_0)}{\partial x_1\partial x_3}\frac{\partial z_1^*(0,0,0)}{\partial\bar{\tau}}\right).
\end{aligned}$$

Calculation of F_3.

$$\frac{\partial^2 f_3}{\partial\alpha\partial\beta}(\bar{\tau},\alpha,\beta) = -\sum_{i=1}^{3}\left[\sum_{j=1}^{3}\frac{\partial^2\Theta_3(\Phi(\eta))}{\partial x_i\partial x_j}\frac{\partial}{\partial\alpha}\Phi_i(\eta)\frac{\partial}{\partial\beta}\Phi_j(\eta) + \frac{\partial\Theta_3(\Phi(\eta))}{\partial x_i}\frac{\partial^2}{\partial\alpha\partial\beta}\Phi_i(\eta)\right](\bar{\tau},\alpha,\beta).$$

We obtain

$$\begin{aligned}
F_3 = &-\frac{\partial^2\Theta_3(\Phi(\tau_0,X_0))}{\partial x_2\partial x_1}\frac{\partial\Phi_2(\tau_0,X_0)}{\partial x_2}\left[\frac{\partial\Phi_1(\tau_0,X_0)}{\partial x_1}\left(-\frac{c_0'}{a_0'}\right) + \frac{\partial\Phi_1(\tau_0,X_0)}{\partial x_3}\right]\\
&-\frac{\partial^2\Theta_3(\Phi(\tau_0,X_0))}{\partial x_3\partial x_1}\frac{\partial\Phi_3(\tau_0,X_0)}{\partial x_2}\left[\frac{\partial\Phi_1(\tau_0,X_0)}{\partial x_1}\left(-\frac{c_0'}{a_0'}\right) + \frac{\partial\Phi_1(\tau_0,X_0)}{\partial x_3}\right]\\
&-\frac{\partial\Theta_3(\Phi(\tau_0,X_0))}{\partial x_2}\left[\frac{\partial^2\Phi_2(\tau_0,X_0)}{\partial x_2\partial x_1}\left(-\frac{c_0'}{a_0'}\right) + \frac{\partial^2\Phi_2(\tau_0,X_0)}{\partial x_2\partial x_3}\right]\\
&-\frac{\partial^2\Theta_3(\Phi(\tau_0,X_0))}{\partial x_1\partial x_3}\frac{\partial\Phi_3(\tau_0,X_0)}{\partial x_3}\left[\frac{\partial\Phi_1(\tau_0,X_0)}{\partial x_1}\left(-\frac{b_0'}{a_0'}\right) + \frac{\partial\Phi_1(\tau_0,X_0)}{\partial x_2}\right]\\
&-\frac{\partial^2\Theta_3(\Phi(\tau_0,X_0))}{\partial x_2\partial x_3}\frac{\partial\Phi_2(\tau_0,X_0)}{\partial x_2}\frac{\partial\Phi_3(\tau_0,X_0)}{\partial x_3} - \frac{\partial^2\Theta_3(\Phi(\tau_0,X_0))}{\partial x_3^2}\frac{\partial\Phi_3(\tau_0,X_0)}{\partial x_2}\frac{\partial\Phi_3(\tau_0,X_0)}{\partial x_3}\\
&-\frac{\partial\Theta_3(\Phi(\tau_0,X_0))}{\partial x_3}\left[\frac{\partial^2\Phi_3(\tau_0,X_0)}{\partial x_2\partial x_1}\left(-\frac{c_0'}{a_0'}\right) + \frac{\partial^2\Phi_3(\tau_0,X_0)}{\partial x_1\partial x_3}\left(-\frac{b_0'}{a_0'}\right) + \frac{\partial^2\Phi_3(\tau_0,X_0)}{\partial x_2\partial x_3}\right].
\end{aligned}$$

7. Classification of hypotheses (H1)-(H11)

To solve system (2.10), we need to know the signs of the coefficients of σ and ρ. So, we solve the first equation, and we obtain either $\rho(\sigma)$ or $\sigma(\rho)$ depending on the coefficients of the first equation of system (2.10). After that we substitute in the second equation which gives an equation of first or second order with respect to either σ or ρ. Finally we obtain three classes:

- **(CL1):** First order system having one solution for ρ and one positive solution for σ, this case corresponds to **(H1), (H5)** and **(H6)**.
- **(CL2):** Second order system having one solution for ρ and one positive solution for σ, this case corresponds to **(H2), (H3), (H4), (H7), (H8)** and **(H9)**.
- **(CL3):** Second order system having either one (**(H10)**) or two (**(H11)**) solutions for ρ and two positive solutions for σ.

8. Appendix D: Applications to the pulsed chemotherapy model

$\frac{\partial\Theta_i(\Phi(\tau_0,X_0))}{\partial x_i} = T_i$, $(i \neq 2)$, $\frac{\partial\Theta_2(\Phi(\tau_0,X_0))}{\partial x_2} = T_2 - R$, $\frac{\partial\Theta_i(\Phi(\tau_0,X_0))}{\partial x_j} = 0$, $(i \neq j$ and $(i,j) \neq (3,2))$,

$$\frac{\partial\Theta_3(\Phi(\tau_0,X_0))}{\partial x_2} = R,\ \frac{\partial\Phi_1(\tau_0,X_0)}{\partial x_1} = T_1^{-2}e^{-r_1\tau_0},\ \frac{\partial\Phi_2(\tau_0,X_0)}{\partial x_2} = T_1^{\frac{-\lambda_2 r_2 k_1}{r_1}} e^{(r_2(1-\lambda_2 k_1)-m)\tau_0},$$

$$\frac{\partial\Phi_3(\tau_0,X_0)}{\partial x_3} = T_1^{\frac{-\lambda_3 r_3 k_1}{r_1}} e^{r_3(1-\lambda_3 k_1)\tau_0},$$

$$\frac{\partial\Phi_3(\tau_0,X_0)}{\partial x_2} = me^{r_3(1-\lambda_3 k_1)\tau_0} T_1^{\frac{-\lambda_3 r_3 k_1}{r_1}} (1-e^{-r_1\tau_0})^{\frac{\lambda_2 r_2 k_1}{r_1}-\frac{\lambda_3 r_3 k_1}{r_1}} \int_0^{\tau_0} e^{-m\mu} I_2(\mu) I_3^{-1}(\mu)d\mu,$$

$$\begin{aligned}\frac{\partial\Phi_1(\tau_0,X_0)}{\partial x_2} = &-\frac{\lambda_1 r_1 k_1 (T_1-e^{-r_1\tau_0})}{T_1^2 e^{r_1\tau_0}(1-e^{-r_1\tau_0})^{2-\frac{\lambda_2 r_2 k_1}{r_1}}} \left[\int_0^{\tau_0} [e^{r_1\mu}(T_1 - e^{-r_1\tau_0}) + (1-T_1)]e^{-m\mu} I_2(\mu)d\mu\right. \\ &\left. + m\int_0^{\tau_0} [e^{r_1\mu}(T_1 - e^{-r_1\tau_0}) + (1-T_1)] I_3(\mu) \left(\int_0^{\mu} e^{-ms} I_2(s) I_3^{-1}(s)ds\right) d\mu\right],\end{aligned}$$

$$\frac{\partial\Phi_1(\tau_0,X_0)}{\partial x_3} = -\frac{\lambda_1 r_1 k_1 (1-e^{-r_1\tau_0})^{\frac{\lambda_3 r_3 k_1}{r_1}} (T_1-e^{-r_1\tau_0})}{T_1^2 e^{r_1\tau_0}(1-e^{-r_1\tau_0})^2} \int_0^{\tau_0} [e^{r_1\mu}(T_1-e^{-r_1\tau_0})+(1-T_1)] I_3(\mu)d\mu,$$

$$a_0' = 1 - T_1^{-1}e^{-r_1\tau_0},$$

$$\begin{aligned}b_0' = &\frac{\lambda_1 r_1 k_1 (T_1-e^{-r_1\tau_0})}{T_1 e^{r_1\tau_0}(1-e^{-r_1\tau_0})^{2-\frac{\lambda_2 r_2 k_1}{r_1}}} \left[\int_0^{\tau_0} [e^{r_1\mu}(T_1 - e^{-r_1\tau_0}) + (1-T_1)]e^{-m\mu} I_2(\mu)d\mu\right. \\ &\left. + m \int_0^{\tau_0} [e^{r_1\mu}(T_1 - e^{-r_1\tau_0}) + (1-T_1)] \left(I_3(\mu)\int_0^{\mu} e^{-ms} I_2(s) I_3^{-1}(s)ds\right) d\mu\right],\end{aligned}$$

$$c_0' = \frac{\lambda_1 r_1 k_1 (T_1-e^{-r_1\tau_0})}{T_1 e^{r_1\tau_0}(1-e^{-r_1\tau_0})^{2-\frac{\lambda_3 r_3 k_1}{r_1}}} \int_0^{\tau_0} [e^{r_1\mu}(T_1 - e^{-r_1\tau_0})) + (1-T_1)] I_3(\mu)d\mu,$$

$$d_0' = 0,\ e_0' = 1 - (T_2 - R)T_1^{-\frac{\lambda_2 r_2 k_1}{r_1}} e^{(r_2(1-\lambda_2 k_1)-m)\tau_0},\ f_0' = 0,\ g_0' = 0,$$

$$h_0' = -RT_1^{\frac{-\lambda_2 r_2 k_1}{r_1}} e^{(r_2(1-\lambda_2 k_1)-m)\tau_0} - \frac{T_3 m e^{r_3(1-\lambda_3 k_1)\tau_0} T_1^{-\frac{\lambda_3 r_3 k_1}{r_1}}}{(1-e^{-r_1\tau_0})^{\frac{\lambda_3 r_3 k_1}{r_1}-\frac{\lambda_2 r_2 k_1}{r_1}}} \int_0^{\tau_0} e^{-m\mu} I_2(\mu) I_3^{-1}(\mu)d\mu,$$

$$i_0' = 1 - T_3 T_1^{-\frac{\lambda_3 r_3 k_1}{r_1}} e^{r_3(1-\lambda_3 k_1)\tau_0},$$

$$\frac{\partial\Phi_1(\tau_0,X_0)}{\partial\bar{\tau}} = \dot{x}_s(\tau_0) = \frac{r_1 k_1 e^{-r_1\tau_0}(T_1-e^{-r_1\tau_0})(1-T_1)}{T_1^2(1-e^{-r_1\tau_0})^2},$$

$$\frac{\partial^2\Phi_2(\tau_0,X_0)}{\partial\bar{\tau}\partial x_2} = \left(r_2 - m - \frac{\lambda_2 r_2 k_1 (T_1-e^{-r_1\tau_0})}{T_1(1-e^{-r_1\tau_0})}\right) T_1^{\frac{-\lambda_2 r_2 k_1}{r_1}} e^{(r_2(1-\lambda_2 k_1)-m)\tau_0},$$

$$\frac{\partial^2\Phi_3(\tau_0,X_0)}{\partial\bar{\tau}\partial x_3} = \left(r_3 - \frac{\lambda_3 r_3 k_1 (T_1-e^{-r_1\tau_0})}{T_1(1-e^{-r_1\tau_0})}\right) T_1^{\frac{-\lambda_3 r_3 k_1}{r_1}} e^{r_3(1-\lambda_3 k_1)\tau_0},$$

$$\begin{aligned}\frac{\partial^2\Phi_3(\tau_0,X_0)}{\partial\bar{\tau}\partial x_2} = &\frac{\left(r_3 - \frac{\lambda_3 r_3 k_1 (T_1-e^{-r_1\tau_0})}{T_1(1-e^{-r_1\tau_0})}\right) me^{r_3(1-\lambda_3 k_1)\tau_0}}{T_1^{\frac{\lambda_3 r_3 k_1}{r_1}}(1-e^{-r_1\tau_0})^{-\frac{\lambda_2 r_2 k_1}{r_1}+\frac{\lambda_3 r_3 k_1}{r_1}}} \int_0^{\tau_0} e^{-m\mu} I_2(\mu) I_3^{-1}(\mu)d\mu \\ &+ m\frac{e^{(r_2(1-\lambda_2 k_1)-m)\tau_0}}{T_1^{\frac{\lambda_2 r_2 k_1}{r_1}}},\end{aligned}$$

$$\frac{\partial^2\Phi_2(\tau_0,X_0)}{\partial x_1\partial x_2} = e^{(r_2(1-\lambda_2 k_1)-m)\tau_0} \lambda_2 r_1^{-1} r_2 T_1^{-1-\frac{\lambda_2 r_2 k_1}{r_1}} (e^{-r_1\tau_0} - 1),$$

$$\begin{aligned}\frac{\partial^2\Phi_2(\tau_0,X_0)}{\partial x_3\partial x_2} = &\frac{r_2 e^{(r_2(1-\lambda_2 k_1)-m)\tau_0}}{T_1^{\frac{\lambda_2 r_2 k_1}{r_1}}(1-e^{-r_1\tau_0})^{-\frac{\lambda_3 r_3 k_1}{r_1}}} \int_0^{\tau_0} \left[(\frac{-1}{k_2} - \lambda_2) I_3(\mu)\right. \\ &\left. + \frac{\lambda_2\lambda_1 r_1 k_1 (T_1-e^{-r_1\tau_0})e^{r_1\mu}}{[e^{r_1\mu}(T_1-e^{-r_1\tau_0})+(1-T_1)]^2} \int_0^{\mu} [e^{r_1 s}(T_1 - e^{-r_1\tau_0}) + (1-T_1)] I_3(s)ds\right] d\mu,\end{aligned}$$

$$\begin{aligned}\frac{\partial^2\Phi_2(\tau_0,X_0)}{\partial x_2^2} = &2e^{(r_2-m-\lambda_2 r_2 k_1)\tau_0} \lambda_2 r_2 \lambda_1 r_1 k_1 (T_1-e^{-r_1\tau_0}) T_1^{-\frac{\lambda_2 r_2 k_1}{r_1}} (1-e^{-r_1\tau_0})^{\frac{\lambda_2 r_2 k_1}{r_1}} \times \\ &\int_0^{\tau_0} \frac{e^{r_1\mu}\int_0^{\mu}[e^{r_1 s}(T_1-e^{-r_1\tau_0})+(1-T_1)]\left[e^{-ms}I_2(s)+mI_3(s)\int_0^s e^{-ml}I_2(l)I_3^{-1}(l)dl\right]ds}{[e^{r_1\mu}(T_1-e^{-r_1\tau_0})+(1-T_1)]^2} d\mu\end{aligned}$$

$$
\begin{aligned}
&- \frac{2r_2 e^{(r_2-m-\lambda_2 r_2 k_1)\tau_0} k_2^{-1}}{(1-e^{-r_1\tau_0})^{-\frac{\lambda_2 r_2 k_1}{r_1}} T_1^{\frac{\lambda_2 r_2 k_1}{r_1}}} \int_0^{\tau_0} e^{-m\mu} I_2(\mu) d\mu \\
&- \frac{2r_2 e^{(r_2-m-\lambda_2 r_2 k_1)\tau_0} (k_2^{-1}+\lambda_2)m}{(1-e^{-r_1\tau_0})^{-\frac{\lambda_2 r_2 k_1}{r_1}} T_1^{\frac{\lambda_2 r_2 k_1}{r_1}}} \int_0^{\tau_0} I_3(\mu)(\textstyle\int_0^{\mu} e^{-ms} I_2(s) I_3^{-1} ds) d\mu,
\end{aligned}
$$

$$
\frac{\partial^2 \Phi_3(\tau_0,X_0)}{\partial x_1 \partial x_3} = e^{r_3(1-\lambda_3 k_1)\tau_0} \lambda_3 r_1^{-1} r_3 T_1^{-1-\frac{\lambda_3 r_3 k_1}{r_1}} (e^{-r_1\tau_0} - 1),
$$

$$
\begin{aligned}
\frac{\partial^2 \Phi_3(\tau_0,X_0)}{\partial x_3^2} &= -2r_3 e^{r_3(1-\lambda_3 k_1)\tau_0} k_3^{-1} T_1^{-\frac{\lambda_3 r_3 k_1}{r_1}} (1-e^{-r_1\tau_0})^{\frac{\lambda_3 r_3 k_1}{r_1}} \int_0^{\tau_0} I_3(\mu) d\mu \\
&+ \int_0^{\tau_0} \frac{2\lambda_3 r_3 k_1 \lambda_1 r_1 e^{r_3(1-\lambda_3 k_1)\tau_0} T_1^{\frac{-\lambda_3 r_3 k_1}{r_1}} (T_1-e^{-r_1\tau_0}) \int_0^{\mu} [e^{r_1 s}(T_1-e^{-r_1\tau_0})+(1-T_1)] I_3(s) ds}{(1-e^{-r_1\tau_0})^{-\frac{\lambda_3 r_3 k_1}{r_1}} e^{-r_1\mu}[e^{r_1\mu}(T_1-e^{-r_1\tau_0})+(1-T_1)]^2} d\mu,
\end{aligned}
$$

$$
\begin{aligned}
\frac{\partial^2 \Phi_3(\tau_0,X_0)}{\partial x_1 \partial x_2} &= -\frac{e^{r_3(1-\lambda_3 r_3 k_1)\tau_0}}{T_1^{\frac{\lambda_3 r_3 k_1}{r_1}} (1-e^{-r_1\tau_0})^{\frac{\lambda_3 r_3 k_1}{r_1}}} \int_0^{\tau_0} \Bigg[\frac{m I_3^{-1}(\mu) \lambda_2 r_2 (T_1-e^{-r_1\tau_0}) e^{-m\mu} (1-e^{r_1\mu}) I_2(\mu)}{r_1 (1-e^{-r_1\tau_0})^{-1-\frac{\lambda_2 r_2 k_1}{r_1}} [e^{r_1\mu}(T_1-e^{-r_1\tau_0})+(1-T_1)]} \\
&+ \frac{\lambda_3 r_3 m e^{r_1\mu} \int_0^{\mu} e^{-ms} I_2(s) I_3^{-1}(s) ds}{(1-e^{-r_1\tau_0})^{-2-\frac{\lambda_2 r_2 k_1}{r_1}} [e^{r_1\mu}(T_1-e^{-r_1\tau_0})+(1-T_1)]^2} \Bigg] d\mu,
\end{aligned}
$$

$$
\begin{aligned}
\frac{\partial^2 \Phi_3(\tau_0,X_0)}{\partial x_2^2} &= \frac{e^{r_3(1-\lambda_3 k_1)\tau_0} T_1^{\frac{-\lambda_3 r_3 k_1}{r_1}}}{(1-e^{-r_1\tau_0})^{\frac{\lambda_3 r_3 k_1}{r_1}}} \int_0^{\tau_0} \Bigg[\frac{2\lambda_3 r_3 m \lambda_1 r_1 k_1 (T_1-e^{-r_1\tau_0}) e^{r_1\mu} \int_0^{\mu} e^{-ms} I_2(s) I_3^{-1}(s) ds}{(1-e^{-r_1\tau_0})^{-\frac{2\lambda_2 r_2 k_1}{r_1}} [e^{r_1\mu}(T_1-e^{-r_1\tau_0})+(1-T_1)]^2} \times \\
&\int_0^{\mu} [e^{r_1 s}(T_1-e^{-r_1\tau_0})+(1-T_1)] \left[e^{-ms} I_2(s) + m I_3(s) \int_0^{s} e^{-ml} I_2(l) I_3^{-1}(l) dl \right] ds \\
&- \frac{2(\lambda_3 r_3 + \frac{r_3}{k_3}) m e^{-m\mu} I_2(\mu) \int_0^{\mu} e^{-ms} I_2(l) I_3^{-1}(l) ds + \frac{2r_3}{k_3} \left(m \int_0^{\mu} e^{-ms} I_2(s) I_3^{-1}(s) ds \right)^2}{(1-e^{-r_1\tau_0})^{-\frac{2\lambda_2 r_2 k_1}{r_1}}} \\
&+ \frac{m 2\lambda_2 r_2 \lambda_1 r_1 k_1 (T_1-e^{-r_1\tau_0}) I_2(\mu) I_3^{-1}(\mu)}{e^{m\mu} (1-e^{-r_1\tau_0})^{-\frac{2\lambda_2 r_2 k_1}{r_1}}} \times \\
&\Bigg(\int_0^{\mu} \frac{\int_0^{s} [e^{r_1 l}(T_1-e^{-r_1\tau_0})+(1-T_1)] \left(e^{-ml} I_2(l) + m I_3(l) \int_0^{l} e^{-mr} I_2(r) I_3^{-1}(r) dr \right) dl}{e^{-r_1 s}[e^{r_1 s}(T_1-e^{-r_1\tau_0})+(1-T_1)]^2} \, ds \\
&- \frac{2r_2}{k_2 (1-e^{-r_1\tau_0})^{-\frac{\lambda_2 r_2 k_1}{r_1}}} \int_0^{\mu} e^{-ms} I_2(s) ds \\
&- \ -\frac{(\lambda_2 r_2 + \frac{r_2}{k_2}) m}{(1-e^{-r_1\tau_0})^{-\frac{\lambda_2 r_2 k_1}{r_1}}} \int_0^{\mu} I_3(s) (\textstyle\int_0^{s} e^{-ml} I_2(l) I_3^{-1}(l) dl) ds \Bigg) \Bigg] d\mu,
\end{aligned}
$$

Case $h_0' \neq 0$, *i.e.* $R + m \neq 0$. We obtain $\frac{\partial \mathsf{z}_1^*}{\partial \bar{\tau}}(0,0) = \frac{r_1 k_1 e^{-r_1\tau_0}(1-T_1)}{(1-e^{-r_1\tau_0})^2}$,

$$
\frac{\partial^2 \mathsf{z}_2^*(0,0)}{\partial \bar{\tau} \partial \alpha} = (1-\lambda_3 k_1) T_3 r_3 T_1^{-\frac{\lambda_3 r_3 k_1}{r_1}} e^{r_3(1-\lambda_3 k_1)\tau_0} h_0'^{-1},
$$

$$
\begin{aligned}
\frac{\partial^2 \mathsf{z}_2^*(0,0)}{\partial \alpha^2} &= \frac{2T_3 r_3 e^{r_3(1-\lambda_3 k_1)\tau_0}}{T_1^{\frac{\lambda_3 r_3 k_1}{r_1}} (1-e^{-r_1\tau_0})^{-\frac{\lambda_3 r_3 k_1}{r_1}} h_0'} \Bigg[\frac{\lambda_3 \lambda_1 k_1 \int_0^{\tau_0} [e^{r_1\mu}(T_1-e^{-r_1\tau_0})+(1-T_1)] I_3(\mu)}{T_1 e^{r_1\tau_0} (1-e^{-r_1\tau_0})} d\mu \\
&- \frac{1}{k_3} \int_0^{\tau_0} I_3(\mu) d\mu + \int_0^{\tau_0} \frac{\lambda_3 \lambda_1 k_1 r_1 (T_1-e^{-r_1\tau_0}) \int_0^{\mu} [e^{r_1 s}(T_1-e^{-r_1\tau_0})+(1-T_1)] I_3(s) ds}{e^{-r_1\mu}[e^{r_1\mu}(T_1-e^{-r_1\tau_0})+(1-T_1)]^2} d\mu \Bigg],
\end{aligned}
$$

$$
\begin{aligned}
\mathcal{D}_2 &= \frac{2(T_2-R) T_3 r_3 e^{r_3(1-\lambda_3 k_1)\tau_0} e^{(r_2-m-r_2\lambda_2 k_1)\tau_0}}{h_0' (1-e^{-r_1\tau_0})^{-\frac{\lambda_3 r_3 k_1}{r_1}} T_1^{\frac{\lambda_2 r_2 k_1}{r_1} + \frac{\lambda_3 r_3 k_1}{r_1}}} \left[r_2 (\frac{1}{k_2} + \lambda_2) \int_0^{\tau_0} I_3(\mu) d\mu \right. \\
&- \frac{r_2 \lambda_2 \lambda_1 k_1}{T_1 e^{r_1\tau_0} (1-e^{-r_1\tau_0})} \int_0^{\tau_0} [e^{r_1\mu}(T_1 - e^{-r_1\tau_0}) + (1-T_1)] I_3(\mu) d\mu
\end{aligned}
$$

$$- r_2\lambda_2\lambda_1 k_1 r_1 (T_1 - e^{-r_1\tau_0})\int_0^{\tau_0} \frac{e^{r_1\mu}\int_0^\mu [e^{r_1 s}(T_1-e^{-r_1\tau_0})+(1-T_1)]I_3(s)ds}{[e^{r_1\mu}(T_1-e^{-r_1\tau_0})+(1-T_1)]^2} d\mu$$

$$- \frac{\lambda_3\lambda_1 k_1(r_2-m-r_2\lambda_2 k_1)}{T_1 e^{r_1\tau_0}(1-e^{-r_1\tau_0})}\int_0^{\tau_0} [e^{r_1\mu}(T_1 - e^{-r_1\tau_0}) + (1-T_1)]I_3(\mu)d\mu$$

$$+ \frac{(r_2-m-r_2\lambda_2 k_1)}{k_3}\int_0^{\tau_0} I_3(\mu)d\mu$$

$$- \frac{\lambda_3\lambda_1 k_1 r_1(r_2-m-r_2\lambda_2 k_1)}{(T_1-e^{-r_1\tau_0})^{-1}}\int_0^{\tau_0} \frac{e^{r_1\mu}\int_0^\mu [e^{r_1 s}(T_1-e^{-r_1\tau_0})+(1-T_1)]I_3(s)ds}{[e^{r_1\mu}(T_1-e^{-r_1\tau_0})+(1-T_1)]^2} d\mu\Bigg],$$

$$\mathcal{B}_2 = -\frac{2(T_2-R)(1-\lambda_3 k_1)T_3 r_3(r_2-m-r_2\lambda_2 k_1)e^{r_3(1-\lambda_3 k_1)\tau_0}e^{(r_2-m-r_2\lambda_2 k_1)\tau_0}}{h_0' T_1^{\frac{\lambda_2 r_2 k_1}{r_1}+\frac{\lambda_3 r_3 k_1}{r_1}}},$$

$$\mathcal{C}_2 = \frac{6(T_2-R)T_3 r_3 r_2 e^{r_3(1-\lambda_3 k_1)\tau_0}e^{(r_2-m-r_2\lambda_2 k_1)\tau_0}(1-e^{-r_1\tau_0})^{2\frac{\lambda_3 r_3 k_1}{r_1}}}{h_0' T_1^{\frac{\lambda_2 r_2 k_1}{r_1}+\frac{\lambda_3 r_3 k_1}{r_1}}}\Bigg[\frac{1}{k_3}\int_0^{\tau_0} I_3(\mu)d\mu$$

$$- \frac{\lambda_3\lambda_1 k_1}{T_1(e^{r_1\tau_0}-1)}\int_0^{\tau_0} [e^{r_1\mu}(T_1 - e^{-r_1\tau_0}) + (1-T_1)]I_3(\mu)d\mu$$

$$- \lambda_3\lambda_1 k_1 r_1(T_1 - e^{-r_1\tau_0})\int_0^{\tau_0} \frac{e^{r_1\mu}\int_0^\mu [e^{r_1 s}(T_1-e^{-r_1\tau_0})+(1-T_1)]I_3(s)ds}{[e^{r_1\mu}(T_1-e^{-r_1\tau_0})+(1-T_1)]^2} d\mu\Bigg] \times$$

$$\Bigg[\frac{\lambda_2\lambda_1 k_1}{T_1(e^{r_1\tau_0}-1)}\int_0^{\tau_0} [e^{r_1\mu}(T_1 - e^{-r_1\tau_0}) + (1-T_1)]I_3(\mu)d\mu - (\tfrac{1}{k_2} + \lambda_2)\int_0^{\tau_0} I_3(\mu)d\mu$$

$$+ \lambda_2\lambda_1 k_1 r_1(T_1 - e^{-r_1\tau_0})\int_0^{\tau_0} \frac{e^{r_1\mu}\int_0^\mu [e^{r_1 s}(T_1-e^{-r_1\tau_0})+(1-T_1)]I_3(s)ds}{[e^{r_1\mu}(T_1-e^{-r_1\tau_0})+(1-T_1)]^2} d\mu\Bigg],$$

Case $h_0' = 0$, *i.e.* $R = m = 0$. We obtain $\frac{\partial z_1^*}{\partial \bar{\tau}}(0,0) = \frac{r_1 k_1 e^{-r_1\tau_0}(1-T_1)}{(1-e^{-r_1\tau_0})^2}$,

$$B_2 = -\frac{2(T_2-R)e^{(r_2-m-\lambda_2 r_2 K_1)\tau_0}\lambda_2 r_2\lambda_1 k_1}{e^{r_1\tau_0}(1-e^{-r_1\tau_0})^{1-\frac{\lambda_2 r_2 k_1}{r_1}} T_1^{1+\frac{\lambda_2 r_2 k_1}{r_1}}}\int_0^{\tau_0} e^{-m\mu}[e^{r_1\mu}(T_1-e^{-r_1\tau_0})+(1-T_1)]I_2(\mu)d\mu$$

$$- \frac{2(T_2-R)me^{(r_2-m-\lambda_2 r_2 K_1)\tau_0}\lambda_2 r_2\lambda_1 k_1}{T_1^{1+\frac{\lambda_2 r_2 k_1}{r_1}} e^{r_1\tau_0}(1-e^{-r_1\tau_0})^{1-\frac{\lambda_2 r_2 k_1}{r_1}}}\int_0^{\tau_0} I_3(\mu)(\int_0^\mu e^{-ms} I_2(s) I_3^{-1}(s)ds)d\mu$$

$$- \frac{2(T_2-R)\lambda_2 r_2\lambda_1 r_1 k_1 e^{(r_2(1-\lambda_2 k_1)-m)\tau_0}}{(T_1-e^{-r_1\tau_0})^{-1} T_1^{\frac{\lambda_2 r_2 k_1}{r_1}}(1-e^{-r_1\tau_0})^{-\frac{\lambda_2 r_2 k_1}{r_1}}}\int_0^{\tau_0} \frac{\int_0^\mu [e^{r_1 s}(T_1-e^{-r_1\tau_0})+(1-T_1)]e^{-ms}I_2(s)ds}{e^{-r_1\mu}[e^{r_1\mu}(T_1-e^{-r_1\tau_0})+(1-T_1)]^2} d\mu$$

$$- \frac{2(T_2-R)\lambda_2 r_2\lambda_1 r_1 k_1 m\int_0^{\tau_0} \frac{\int_0^\mu [e^{r_1 s}(T_1-e^{-r_1\tau_0})+(1-T_1)]I_3(s)(\int_0^s e^{-ml}I_2(l)I_3^{-1}(l)dl)ds}{e^{-r_1\mu}[e^{r_1\mu}(T_1-e^{-r_1\tau_0})+(1-T_1)]^2} d\mu}{e^{-(r_2(1-\lambda_2 k_1)-m)\tau_0}(T_1-e^{-r_1\tau_0})^{-1} T_1^{\frac{\lambda_2 r_2 k_1}{r_1}}(1-e^{-r_1\tau_0})^{-\frac{\lambda_2 r_2 k_1}{r_1}}}$$

$$+ \frac{2(T_2-R)r_2 e^{(r_2(1-\lambda_2 k_1)-m)\tau_0}}{k_2 T_1^{\frac{\lambda_2 r_2 k_1}{r_1}}(1-e^{-r_1\tau_0})^{-\frac{\lambda_2 r_2 k_1}{r_1}}}\int_0^{\tau_0} e^{-m\mu} I_2(\mu)d\mu$$

$$+ \frac{2(T_2-R)r_2(\frac{1}{k_2}+\lambda_2)me^{(r_2(1-\lambda_2 k_1)-m)\tau_0}}{T_1^{\frac{\lambda_2 r_2 k_1}{r_1}}(1-e^{-r_1\tau_0})^{\frac{-\lambda_2 r_2 k_1}{r_1}}}\int_0^{\tau_0} I_3(\mu)(\int_0^\mu e^{-ms} I_2(s) I_3^{-1}(s)ds)d\mu,$$

$$D_2 = -(T_2 - R)(r_2 - m - \lambda_2 r_2 k_1)T_1^{-\frac{\lambda_2 r_2 k_1}{r_1}} e^{(r_2-m-\lambda_2 r_2 k_1)\tau_0},$$

$$F_2 = -(T_2 - R)\Bigg[\frac{r_2 e^{(r_2-m-\lambda_2 r_2 k_1)\tau_0}(-\frac{1}{k_2}-\lambda_2)}{T_1^{\frac{\lambda_2 r_2 k_1}{r_1}}(1-e^{-r_1\tau_0})^{-\frac{\lambda_3 r_3 k_1}{r_1}}}\int_0^{\tau_0} I_3(\mu)d\mu$$

$$+ \frac{\lambda_2 r_2\lambda_1 r_1 k_1 e^{(r_2-m-\lambda_2 r_2 k_1)\tau_0}(T_1-e^{-r_1\tau_0})}{(1-e^{-r_1\tau_0})^{-\frac{\lambda_3 r_3 k_1}{r_1}} T_1^{\frac{\lambda_2 r_2 k_1}{r_1}}}\int_0^{\tau_0} \frac{e^{r_1\mu}\int_0^\mu [e^{r_1 s}(T_1-e^{-r_1\tau_0})+(1-T_1)]I_3(s)ds}{[e^{r_1\mu}(T_1-e^{-r_1\tau_0})+(1-T_1)]^2} d\mu$$

$$+ \frac{\lambda_2\lambda_1 r_2 k_1 e^{(r_2-m-\lambda_2 r_2 k_1)\tau_0}}{e^{r_1\tau_0}(1-e^{-r_1\tau_0})^{1-\frac{\lambda_3 r_3 k_1}{r_1}} T_1^{1+\frac{\lambda_2 r_2 k_1}{r_1}}}\int_0^{\tau_0} [e^{r_1\mu}(T_1 - e^{-r_1\tau_0}) + (1-T_1)]I_3(\mu)d\mu\Bigg],$$

$B_3 = 0$, $D_3 = 0$,

$$
\begin{aligned}
C_3 = -T_3 \Bigg[& \frac{2\lambda_3\lambda_1 r_3 k_1 e^{r_3(1-\lambda_3 k_1)\tau_0}}{e^{r_1\tau_0} T_1^{1+\frac{\lambda_3 r_3 k_1}{r_1}} (1-e^{-r_1\tau_0})^{1-\frac{\lambda_3 r_3 K_1}{r_1}}} \int_0^{\tau_0} I_3(\mu)[e^{r_1\mu}(T_1-e^{-r_1\tau_0})+(1-T_1)]d\mu \\
& - \frac{2r_3 e^{r_3(1-\lambda_3 k_1)\tau_0}}{k_3 T_1^{\frac{\lambda_3 r_3 k_1}{r_1}} (1-e^{-r_1\tau_0})^{-\frac{\lambda_3 r_3 k_1}{r_1}}} \int_0^{\tau_0} I_3(\mu) d\mu \\
& + \frac{2\lambda_3\lambda_1 r_3 k_1 r_1 e^{r_3(1-\lambda_3 k_1)\tau_0}(T_1-e^{-r_1\tau_0})}{T_1^{\frac{\lambda_3 r_3 k_1}{r_1}} (1-e^{-r_1\tau_0})^{-\frac{\lambda_3 r_3 k_1}{r_1}}} \int_0^{\tau_0} \frac{e^{r_1\mu} \int_0^\mu I_3(s)[e^{r_1 s}(T_1-e^{-r_1\tau_0})+(1-T_1)]ds}{[e^{r_1\mu}(T_1-e^{-r_1\tau_0})+(1-T_1)]^2} d\mu \Bigg],
\end{aligned}
$$

$$
E_3 = -T_3 r_3 (1-\lambda_3 k_1) T_1^{-\frac{\lambda_3 r_3 k_1}{r_1}} e^{r_3(1-\lambda_3 k_1)\tau_0},
$$

$$
\begin{aligned}
F_3 = & -\frac{T_3 e^{r_3(1-\lambda_3 k_1)\tau_0} r_3 \lambda_3 \lambda_1 k_1 e^{-r_1\tau_0}}{T_1^{1+\frac{\lambda_3 r_3 K_1}{r_1}} (1-e^{-r_1\tau_0})^{1-\frac{\lambda_2 r_2 k_1}{r_1}}} \int_0^{\tau_0} [e^{r_1\mu}(T_1 - e^{-r_1\tau_0}) + (1-T_1)] I_2(\mu) d\mu \\
& - \frac{T_3 r_3 \lambda_3 \lambda_1 r_1 k_1 (T_1-e^{-r_1\tau_0}) T_1^{-\frac{\lambda_3 r_3 k_1}{r_1}}}{e^{-r_3(1-\lambda_3 k_1)\tau_0} (1-e^{-r_1\tau_0})^{-\frac{\lambda_2 r_2 k_1}{r_1}}} \int_0^{\tau_0} \frac{e^{r_1\mu} \int_0^\mu [e^{r_1 s}(T_1-e^{-r_1\tau_0})+(1-T_1)] I_2(s) ds}{[e^{r_1\mu}(T_1-e^{-r_1\tau_0})+(1-T_1)]^2} d\mu \\
& + T_3 r_3 T_1^{-\frac{\lambda_3 r_3 k_1}{r_1}} e^{r_3(1-\lambda_3 k_1)\tau_0} (1-e^{-r_1\tau_0})^{\frac{\lambda_2 r_2 k_1}{r_1}} (\frac{1}{k_3} + \lambda_3) \int_0^{\tau_0} I_2(\mu) d\mu.
\end{aligned}
$$

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