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PULSED CHEMOTHERAPY MODEL

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ABSTRACT. A mathematical model for cell population with resistant tumor is studied in this work. A periodic chemotherapeutic treatment is considered. We study the stability of the trivial periodic solutions and bifurcation of nontrivial periodic solutions by the mean of bifurcation analysis.

1. INTRODUCTION

In this work a mathematical model for cancer chemotherapy is studied by considering normal-tumor cell interactions. Our work is inspired from papers [5] and [8], where the authors consider some interactions between normal and tumor cells. The model studied here is derived from Panetta [8] where normal and cancerous cells are in interaction, and the treatment considered there acts instantaneously on all kinds of cells. The mathematical model obtained is a system of impulsive differential equations. Numerical analysis of the Panetta model [8] is considered in [10], where the role of the initial tumor biomass on the evolution of the tumor is studied.
In Panetta [8] two cancer models with resistant tumor cells are discussed, the first one with acquired resistance and the second one with reduced resistance. In this paper we study a model including both the acquired resistance and reduced resistance given by

$$\dot{x}_1(t) = r_1 x_1 \left(1 - \frac{x_1}{K_1} - \lambda_1(x_2 + x_3)\right), \tag{1}$$

$$\dot{x}_2(t) = r_2 x_2 \left(1 - \frac{x_2 + x_3}{K_2} - \lambda_2(x_1 + x_3)\right) - m x_2, \tag{2}$$

$$\dot{x}_3(t) = r_3 x_3 \left(1 - \frac{x_2 + x_3}{K_3} - \lambda_3(x_1 + x_2)\right) + m x_2, \tag{3}$$

$$x_1(t_i^+) = T_1 x_1(t_i), \tag{4}$$

$$x_2(t_i^+) = (T_2 - R) x_2(t_i), \tag{5}$$

$$x_3(t_i^+) = T_3 x_3(t_i) + R x_2(t_i), \tag{6}$$

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where $t_{i+1} - t_i = \tau > 0$, $\forall i \in \mathbb{N}$, and for $j = \overline{1,3}$, T_j, R are positive constants.
The variables and the parameters are
m: acquired resistance parameter, usually it is very small (see [7]),
r_1, r_2, r_3: growth rates of the normal, sensitive tumor and resistant tumor cells respectively,
K_1, K_2, K_3 : carrying capacities of the normal, sensitive tumor and resistant tumor cells respectively,
λ_1, λ_2, λ_3: competitive parameters of the normal, sensitive tumor and resistant tumor cells respectively,
τ: period of drug dose administration,
T_1, T_2, T_3: survival fractions of normal, sensitive tumor and resistant tumor cells respectively.
R: fraction of cells mutating due to the drug dose which is less than T_2.
Some recent works have considered models similar to (1)-(6), see for instance [2], [4], [6] and [9].
We give our main results in the next section, first stability of fixed point solutions and bifurcation analysis are discussed, next the results obtained are applied to the model (1)-(6). Conclusions are given in the third section, in section four we give appendix.

2. Main results

In this section we consider the following system

$$\begin{aligned}
\dot{x}_1(t) &= F_1(x_1(t), x_2(t), x_3(t)), && (7)\\
\dot{x}_2(t) &= F_2(x_1(t), x_2(t), x_3(t)), && (8)\\
\dot{x}_3(t) &= F_3(x_1(t), x_2(t), x_3(t)), && (9)\\
x_1(t_i^+) &= \Theta_1(x_1(t_i), x_2(t_i), x_3(t_i)), && (10)\\
x_2(t_i^+) &= \Theta_2(x_1(t_i), x_2(t_i), x_3(t_i)), && (11)\\
x_3(t_i^+) &= \Theta_3(x_1(t_i), x_2(t_i), x_3(t_i)), && (12)
\end{aligned}$$

where $t_{i+1} - t_i = cste = \tau > 0$ $\forall i \in \mathbb{N}$, $x_j \in \mathbb{R}$ and Θ_j is positive smooth function, for $j = \overline{1,3}$.
The analysis of (7)-(12) allows us to obtain results applicable to the model (1)-(6).
Variables and functions of (7)-(12) are the following:
τ : period between two successive drug treatment,
x_j : normal (resp. sensitive tumor and resistant tumor) cell biomass, for $j = 1$ (resp. 2, 3),
$\Theta_j(x_1(t_i), x_2(t_i), x_3(t_i))$: fraction of normal (resp. sensitive tumor, resistant tumor) cells, surviving the i^{th} drug treatment, for $j = 1$ (resp. 2, 3),
$F_j(x_1, x_2, x_3)$: biomass growth of normal (resp. sensitive tumor, resistant tumor) cells for $j = 1$ (resp. 2, 3).
In our study, we first consider the unperturbed problem $\dot{x_1} = F_1(x_1, 0, 0)$, with periodic impulses $x_1(n\tau^+) = \Theta_1(x_1(n\tau), 0, 0)$. We assume that the one dimensional equation (7) with impulse equations (10)-(12) has a periodic stable solution (see [5],[8]). It is called a trivial solution and could correspond to a preventive treatment. However, from clinical point of view such a treatment is not a warranty that no tumor can develop.
We consider the onset of a tumor in a patient who is under preventive treatment

and the displacement of the equilibrium from a situation without cancer cells to one with a significant fraction of them, this corresponds to a bifurcation from a stable equilibrium. We study the dependence of the equilibrium on the time period τ between two drug injections.

A solution $\xi = (x_1, x_2, x_3)$ of the problem (7)-(12) is a function defined on $\mathbb{R}_+$ with nonnegative components continuously differentiable in $\mathbb{R}_+ - \{t_i\}_{i\geq 0}$ with $t_0 = 0$, and satisfying all of the relations (7) through (12).

ξ is called a trivial solution of problem (7)-(12) if its second and third components are zeros, otherwise it is a nontrivial solution. Also, ξ is called trivial (resp. nontrivial) τ-periodic solution if it is a trivial (resp. nontrivial) solution with $\xi(n\tau) = \xi((n+1)\tau)$ for all $n \geq 0$.

In our study, we consider that $\Theta = (\Theta_1, \Theta_2, \Theta_3)$ is positive and that the positive octant is invariant with respect to the flow Φ associated to (7)-(9). The functions $F = (F_1, F_2, F_3)$ and Θ are assumed smooth enough. Finally, we suppose that $F_2(x_1, 0, x_3) \equiv \Theta_2(x_1, 0, x_3) \equiv 0$, $F_3(x_1, 0, 0) \equiv \Theta_3(x_1, 0, 0) \equiv 0$ and $\Theta_i(X) \neq 0$ ($X \in \mathbb{R}^3_+$) for $x_i \neq 0$, $i = 1, 2, 3$. Our main objective is to study the stability of the trivial periodic solutions with non negative components, the loss of stability for some values of the parameters, and the onset of positive nontrivial periodic solutions as a consequence of this lost.

We have

$$\xi(t) = \Phi(t, X_0), 0 < t \leq \tau, \tag{13}$$

where $\xi(0) = X_0$. We assume that the flow Φ applies up to time τ. So, $\xi(\tau) = \Phi(\tau, X_0)$. Then, within a very small time interval starting at time τ, we assume that the treatment is administered and kills instantaneously a fraction of the population. The term $\xi(\tau^+)$ denote the state of the population after the treatment, $\xi(\tau^+)$ is determined in terms of $\xi(\tau)$ according to equations (10)-(12). We have $\xi(\tau^+) = \Theta(\xi(\tau)) = \Theta(\Phi(\tau, X_0))$.

Let Ψ be the operator defined by

$$\Psi(\tau, X_0) = \Theta(\Phi(\tau, X_0)), \tag{14}$$

and denote by $D_X\Psi$ the derivative of Ψ with respect to X. Then $\xi = \Phi(., X_0)$ is a τ-periodic solution of (7)-(12) if and only if

$$\Psi(\tau, X_0) = X_0, \tag{15}$$

i.e. X_0 is a fixed point of $\Psi(\tau, .)$, and it is exponentially stable if and only if the spectral radius $\rho(D_X\Psi(\tau, .))$ is strictly less than 1 ([3]). A fixed point X_0 of $\Psi(\tau, .)$ is the initial state of (7)-(12) which gives a τ-periodic solution ξ verifying $\xi(0) = X_0$. Consequently, for each fixed point X_0 of $\Psi(\tau, .)$ there is an associated τ-periodic solution ξ and vice versa.

Remark 1 We say that a fixed point is trivial if it is associated to a trivial periodic solution. The fixed point of $\Psi(\tau, .)$ can be determined using a fixed point method with some additional conditions on F and Θ assumed smooth enough ([3]).

If $x_2 = x_3 = 0$ the problem (7), (10) has a τ_0-periodic solution denoted x_s, it is assumed stable, *i.e*

$$\left| \frac{\partial \Theta_1}{\partial x_1}(\Phi(\tau_0, (x_0, 0, 0))) \frac{\partial \Phi_1}{\partial x_1}(\tau_0, (x_0, 0, 0)) \right| < 1. \tag{16}$$

The function $\zeta = (x_s, 0, 0)$ is a trivial solution of $(7) - (12)$, and $\zeta_0 = \zeta(0) = (x_s(0), 0, 0)$ is a fixed point solution of (15).

2.1. **Stability of the fixed point** ζ_0**.** Denote $x_0 = x_s(0)$, then $(x_0, 0, 0)$ is the initial condition for ζ, that is $\zeta(0) = (x_0, 0, 0)$.
We have $D_X\Psi(\tau_0, X) = D_X\Theta(\Phi(\tau_0, X))\dfrac{\partial \Phi}{\partial X}(\tau_0, X)$, then for $X_0 = (x_0, 0, 0)$ we obtain

$$D_X\Psi(\tau_0, X_0) = D_X\Theta(\Phi(\tau_0, X_0))\tfrac{\partial \Phi}{\partial X}(\tau_0, X_0)$$

$$= \begin{pmatrix} \frac{\partial\Theta_1(\Phi(\tau_0,X_0))}{\partial x_1} & \frac{\partial\Theta_1(\Phi(\tau_0,X_0))}{\partial x_2} & \frac{\partial\Theta_1(\Phi(\tau_0,X_0))}{\partial x_3} \\ 0 & \frac{\partial\Theta_2(\Phi(\tau_0,X_0))}{\partial x_2} & 0 \\ 0 & \frac{\partial\Theta_3(\Phi(\tau_0,X_0))}{\partial x_2} & \frac{\partial\Theta_3(\Phi(\tau_0,X_0))}{\partial x_3} \end{pmatrix} \begin{pmatrix} \frac{\partial\Phi_1(\tau_0,X_0)}{\partial x_1} & \frac{\partial\Phi_1(\tau_0,X_0)}{\partial x_2} & \frac{\partial\Phi_1(\tau_0,X_0)}{\partial x_3} \\ 0 & \frac{\partial\Phi_2(\tau_0,X_0)}{\partial x_2} & 0 \\ 0 & \frac{\partial\Phi_3(\tau_0,X_0)}{\partial x_2} & \frac{\partial\Phi_3(\tau_0,X_0)}{\partial x_3} \end{pmatrix}$$

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

The solution ζ is exponentially stable if and only if the spectral radius is less than one, that is

$$\left|\frac{\partial\Theta_j}{\partial x_j}(\Phi(\tau_0, X_0))\frac{\partial\Phi_j}{\partial x_j}(\tau_0, X_0)\right| < 1, \text{ for } j = 1, 2, 3.$$

Consider the variational equation associated to the system (7)-(9)

$$\frac{d}{dt}(D_X\Phi(t, X_0)) = D_XF(\Phi(t, X_0))(D_X\Phi(t, X_0)), \tag{17}$$

with the initial condition is $D_X\Phi(0, X_0) = Id_{\mathbb{R}^3}$.
We obtain $\dfrac{\partial\Phi_1(t, X_0)}{\partial x_1} = e^{\int_0^t \frac{\partial F_1(\zeta(r))}{\partial x_1}dr}$, $\dfrac{\partial\Phi_2(t, X_0)}{\partial x_2} = e^{\int_0^t \frac{\partial F_2(\zeta(r))}{\partial x_2}dr}$ and $\dfrac{\partial\Phi_3(t, X_0)}{\partial x_3} = e^{\int_0^t \frac{\partial F_3(\zeta(r))}{\partial x_3}dr}$ for $0 \le t < \tau_0$.
We have the following result

Theorem 1 If conditions $\left|\dfrac{\partial\Theta_j}{\partial x_j}(\zeta(\tau_0))\right| e^{\int_0^{\tau_0} \frac{\partial F_j}{\partial x_j}(\zeta(r))dr} < 1$ for $j = 1, 2, 3$ are satisfied, then the trivial solution $\zeta = (x_s, 0, 0)$ is exponentially stable.

2.2. **Critical cases.** In this section, we analyze the bifurcation of nontrivial periodic solutions of system $(7) - (12)$ near ζ. Let $\bar{\tau}$ and $\bar{X}$ such that $\tau = \tau_0 + \bar{\tau}$ and $X = X_0 + \bar{X}$. The equation (15) is equivalent to

$$M(\bar{\tau}, \bar{X}) = 0, \tag{18}$$

where $M(\bar{\tau}, \bar{X}) = \big(M_1(\bar{\tau}, \bar{X}), M_2(\bar{\tau}, \bar{X}), M_3(\bar{\tau}, \bar{X})\big) = X_0 + \bar{X} - \Psi(\tau_0 + \bar{\tau}, X_0 + \bar{X})$.
If $(\bar{\tau}, \bar{X})$ is a zero of M, then $(X_0 + \bar{X})$ is a fixed point of $\Psi(\tau_0 + \bar{\tau}, .)$. Since ζ is a trivial τ_0-periodic solution (7)-(12), then it is associated to the trivial fixed point X_0 of $\Psi(\tau_0, .)$. From the stability of the solution x_s in the one dimensional space, we have

$$1 - \left|\frac{\partial\Theta_1}{\partial x_1}(\zeta(\tau_0))\right| \left|\frac{\partial\Phi_1}{\partial x_1}(\tau_0, (x_0, 0, 0))\right| \neq 0. \tag{19}$$

From (19) and the implicit function theorem, we have a branch of trivial τ_0- periodic solutions of (7)-(12). Let

$$D_X M(\bar{\tau}, \bar{X}) = \begin{pmatrix} \acute{a} & \acute{b} & \acute{c} \\ \acute{d} & \acute{e} & \acute{f} \\ \acute{g} & \acute{h} & \acute{i} \end{pmatrix} \tag{20}$$

with $\acute{a} = \acute{a}_0$, $\acute{b} = \acute{b}_0$, $\acute{c} = \acute{c}_0$, $\acute{d} = \acute{d}_0$, $\acute{e} = \acute{e}_0$, $\acute{f} = \acute{f}_0$, $\acute{g} = \acute{g}_0$, $\acute{h} = \acute{h}_0$ and $\acute{i} = \acute{i}_0$, for $(\bar{\tau}, \bar{X}) = (0,(0,0,0))$. We have $\acute{d}_0 = 0$, $\acute{f}_0 = 0$, $\acute{g}_0 = 0$ and $\acute{a}_0 > 0$.
A necessary condition for the bifurcation of non trivial zeros of the function M is that the determinant of the Jacobian matrix $D_X M(0,(0,0,0))$ be equal to zero, that is $\acute{e}_0.\acute{i}_0 = 0$.
There are three critical cases: **(C1)** $\acute{e}_0 = 0$ and $\acute{i}_0 \neq 0$, **(C2)** $\acute{e}_0 \neq 0$ and $\acute{i}_0 = 0$, and **(C3)** $\acute{e}_0 = 0$ and $\acute{i}_0 = 0$.
Now, we analyze the possible bifurcation in all cases.
(C1): For $\acute{e}_0 = 0$ and $\acute{i}_0 \neq 0$, we have $M(0,(0,0,0)) = 0$. Let $D_X M(0,(0,0,0)) = E$, then $\dim\ker(E) = \operatorname{co}\dim \mathrm{R(E)} = 1$. Denote by P and Q the projectors onto $\ker(E)$ and $R(E)$ respectively, such that $P + Q = Id_{\mathbb{R}^3}$,
$P\mathbb{R}^3 = \mathrm{span}\{\mathrm{Y}_0\} = \ker(\mathrm{E})$, with $Y_0 = \left(\frac{\acute{c}_0\acute{h}_0}{\acute{a}_0\acute{i}_0} - \frac{\acute{b}_0}{\acute{a}_0}, 1, -\frac{\acute{h}_0}{\acute{i}_0}\right)$ and
$Q\mathbb{R}^3 = \mathrm{span}\{(1,0,0),(0,0,1)\} = R(E)$.
Then $(I-P)\mathbb{R}^3 = \mathrm{span}\{(1,0,0),(0,0,1)\}$ and $(I-Q)\mathbb{R}^3 = \mathrm{span}\{(0,1,0)\}$.
Equation (18) is equivalent to

$$\begin{cases} M_1(\bar{\tau}, \alpha Y_0 + Z) &= 0, \\ M_2(\bar{\tau}, \alpha Y_0 + Z) &= 0, \\ M_3(\bar{\tau}, \alpha Y_0 + Z) &= 0, \end{cases} \tag{21}$$

where $Z = (z_1, 0, z_3)$, $(\bar{\tau}, \bar{X}) = (\bar{\tau}, \alpha Y_0 + Z)$ and $(\alpha, z_1, z_3) \in \mathbb{R}^3$.
From the first and last equations of (21), we have

$$\det \begin{pmatrix} \frac{\partial M_1(0,(0,0,0))}{\partial z_1} & \frac{\partial M_1(0,(0,0,0))}{\partial z_3} \\ \frac{\partial M_3(0,(0,0,0))}{\partial z_1} & \frac{\partial M_3(0,(0,0,0))}{\partial z_3} \end{pmatrix} = \det \begin{pmatrix} \acute{a}_0 & \acute{c}_0 \\ 0 & \acute{i}_0 \end{pmatrix} = \acute{a}_0.\acute{i}_0 \neq 0.$$

From the implicit function theorem, there exist $\delta > 0$ sufficiently small and a unique continuous function Z^*, such that $Z^*(\bar{\tau}, \alpha) = (z_1^*(\bar{\tau}, \alpha), 0, z_3^*(\bar{\tau}, \alpha))$, $Z^*(0,0) = (0,0,0)$,

$$M_1\left(\bar{\tau}, \left(\left(\frac{\acute{c}_0\acute{h}_0}{\acute{a}_0\acute{i}_0} - \frac{\acute{b}_0}{\acute{a}_0}\right)\alpha + z_1^*(\bar{\tau}, \alpha), \alpha, -\frac{\acute{h}_0}{\acute{i}_0}\alpha + z_3^*(\bar{\tau}, \alpha)\right)\right) = 0 \tag{22}$$

and

$$M_3\left(\bar{\tau}, \left(\left(\frac{\acute{c}_0\acute{h}_0}{\acute{a}_0\acute{i}_0} - \frac{\acute{b}_0}{\acute{a}_0}\right)\alpha + z_1^*(\bar{\tau}, \alpha), \alpha, -\frac{\acute{h}_0}{\acute{i}_0}\alpha + z_3^*(\bar{\tau}, \alpha)\right)\right) = 0, \tag{23}$$

for every $(\bar{\tau}, \alpha)$ such that $|\alpha| < \delta$ and $|\bar{\tau}| < \delta$.
Moreover, we have $\frac{\partial Z^*}{\partial \alpha}(0,0) = (0,0,0)$.
Then $M(\bar{\tau}, \bar{X}) = 0$ if and only if

$$f_2(\bar{\tau}, \alpha) = M_2\left(\bar{\tau}, \left(\left(\frac{\acute{c}_0\acute{h}_0}{\acute{a}_0\acute{i}_0} - \frac{\acute{b}_0}{\acute{a}_0}\right)\alpha + z_1^*(\bar{\tau}, \alpha), \alpha, -\frac{\acute{h}_0}{\acute{i}_0}\alpha + z_3^*(\bar{\tau}, \alpha)\right)\right) = 0. \tag{24}$$

Equation (24) is called determining equation and the number of its solutions is equal to the number of periodic solutions of (7)-(12) (see [1]). We now proceed to solving equation (24).
First, it is easy to see that $f_2(0,0) = 0$.
From the Taylor development of f_2 around $(\bar{\tau}, \alpha) = (0,0)$, we find that $\frac{\partial f_2(0,0)}{\partial \bar{\tau}} = \frac{\partial f_2(0,0)}{\partial \alpha} = 0$.
Let $A_2 = \frac{\partial^2 f_2(0,0)}{\partial \bar{\tau}^2}$, $B_2 = \frac{\partial^2 f_2(0,0)}{\partial \bar{\tau} \partial \alpha}$ and $C_2 = \frac{\partial^2 f_2(0,0)}{\partial \alpha^2}$. It's shown that $A_2 = 0$. Hence

$$f_2(\bar{\tau}, \alpha) = B_2 \bar{\tau} \alpha + C_2 \frac{\alpha^2}{2} + o\left(|\alpha|^2 + |\bar{\tau}|^2\right).$$

By taking $\bar{\tau} = \sigma\alpha$, we have $f_2(\sigma\alpha, \alpha) = \frac{\alpha^2}{2} g_2(\sigma, \alpha)$ where $g_2(\sigma, \alpha) = 2B_2\sigma + C_2 + o_\alpha\left(1 + \sigma^2\right)$. Further $\frac{\partial g_2}{\partial \sigma}(\sigma, 0) = 2B_2$ and $g_2(\sigma, 0) = 2B_2\sigma + C_2$. So, for $B_2 \neq 0$ and $\sigma_0 = -\frac{C_2}{2B_2}$ we have $g_2(\sigma_0, 0) = 0$ and $\frac{\partial g_2}{\partial \sigma}(\sigma_0, 0) \neq 0$, using the implicit function theorem we find a function $\sigma(\alpha)$ such that for α small enough $g_2(\sigma(\alpha), \alpha) = 0$ and $\sigma(0) = \sigma_0 = -\frac{C_2}{2B_2}$.
Then, for α near 0 and $\bar{\tau}(\alpha) = \sigma(\alpha)\alpha$ we have $f_2(\bar{\tau}(\alpha), \alpha) = 0$.
Remark 2 As mentioned above, we are interested only on positive solutions, *i.e.* solutions with positive components, so all the components of the term $X_0 + \bar{X} = X_0 + \alpha Y_0 + Z^*(\bar{\tau}(\alpha), \alpha)$ must be nonnegative, then we must have $\alpha \geq 0$, $-\frac{\acute{h}_0}{\acute{i}_0}\alpha + z_3^*(\bar{\tau}(\alpha), \alpha) \geq 0$ and $\tau_0 + \bar{\tau}(\alpha) > 0$. These conditions are satisfied for $\frac{\acute{h}_0}{\acute{i}_0} \leq 0$ and $\alpha (\geq 0)$ small enough, since $z_3^*(0,0) = \frac{\partial z_3^*(0,0)}{\partial \bar{\tau}} = \frac{\partial z_3^*(0,0)}{\partial \alpha} = 0$.
In conclusion we have the following theorem.
Theorem 2 Let $\left|\frac{\partial \Theta_j}{\partial x_j}(\zeta(\tau_0))\right| e^{\int_0^{\tau_0} \frac{\partial F_j}{\partial x_j}(\zeta(r))dr} < 1$ for $j = 1, 3$ and $\left|\frac{\partial \Theta_2}{\partial x_2}(\zeta(\tau_0))\right| e^{\int_0^{\tau_0} \frac{\partial F_2}{\partial x_2}(\zeta(r))dr} = 1$, we have the following results:
a) If $B_2C_2 \neq 0$ we have a bifurcation of nontrivial periodic solutions of (7)-(12) with period $\tau(\alpha) = \tau_0 + \bar{\tau}(\alpha)$ starting from $X_0 + \alpha Y_0 + Z^*(\bar{\tau}(\alpha), \alpha)$ for all $\alpha (> 0)$ small enough, moreover $\bar{\tau}(\alpha) \simeq -\dfrac{C_2}{2B_2}\alpha$. Consequently, we have a supercritical bifurcation if $B_2C_2 < 0$ and a subcritical cases if $B_2C_2 > 0$.
b) If $B_2C_2 = 0$ we have an undetermined cases.
(C2): For $\acute{e}_0 \neq 0$ and $\acute{i}_0 = 0$, we have $M(0, (0,0,0)) = 0$. Let $D_X M(0, (0,0,0)) = E$, then $\dim\ker(E) = \operatorname{co}\dim \mathrm{R(E)} = 1$. For this case we take $Y_0 = \left(\dfrac{-\acute{c}_0}{\acute{a}_0}, 0, 1\right)$ and $Q\mathbb{R}^3 = \operatorname{span}\left\{(1,0,0), \left(0, 1, \dfrac{\acute{h}_0}{\acute{e}_0}\right)\right\} = R(E)$.
Then $(I-P)\mathbb{R}^3 = \operatorname{span}\{(1,0,0),(0,1,0)\}$ and $(I-Q)\mathbb{R}^3 = \operatorname{span}\{(0,0,1)\}$.
Let $Z = (z_1, z_2, 0)$, $(\bar{\tau}, \bar{X}) = (\bar{\tau}, \alpha Y_0 + Z)$ and $(\alpha, z_1, z_2) \in \mathbb{R}^3$.
From the first and second equations of (21), we have

$$\det\begin{pmatrix} \frac{\partial M_1(0,(0,0,0))}{\partial z_1} & \frac{\partial M_1(0,(0,0,0))}{\partial z_2} \\ \frac{\partial M_2(0,(0,0,0))}{\partial z_1} & \frac{\partial M_2(0,(0,0,0))}{\partial z_2} \end{pmatrix} = \det\begin{pmatrix} \acute{a}_0 & \acute{b}_0 \\ 0 & \acute{e}_0 \end{pmatrix} = \acute{a}_0.\acute{e}_0 \neq 0.$$

By the implicit function theorem, there exist $\delta > 0$ sufficiently small and a unique continuous function Z^*, such that $Z^*(\bar{\tau}, \alpha) = (z_1^*(\bar{\tau}, \alpha), z_2^*(\bar{\tau}, \alpha), 0)$, $Z^*(0,0) =$

$(0,0,0)$,

$$M_1\left(\bar{\tau},\left(-\frac{\acute{c}_0}{\acute{a}_0}\alpha+z_1^*(\bar{\tau},\alpha),z_2^*(\bar{\tau},\alpha),\alpha\right)\right)=0 \tag{25}$$

and

$$M_2\left(\bar{\tau},\left(-\frac{\acute{c}_0}{\acute{a}_0}\alpha+z_1^*(\bar{\tau},\alpha),z_2^*(\bar{\tau},\alpha),\alpha\right)\right)=0, \tag{26}$$

for every $(\bar{\tau},\alpha)$ such that $|\alpha|<\delta$ and $|\bar{\tau}|<\delta$.
Moreover $\dfrac{\partial Z^*}{\partial\alpha}(0,0)=(0,0,0)$.
Then $M(\bar{\tau},\bar{X})=0$ if and only if

$$f_3(\bar{\tau},\alpha)=M_3\left(\bar{\tau},\left(-\frac{\acute{c}_0}{\acute{a}_0}\alpha+z_1^*(\bar{\tau},\alpha),z_2^*(\bar{\tau},\alpha),\alpha\right)\right)=0.$$

We obtain $f_3(\bar{\tau},\alpha) \;=\; B_3\bar{\tau}\alpha+C_3\frac{\alpha^2}{2}+o\left((|\alpha|+|\bar{\tau}|)^2\right)$.
Using the same arguments as in the case **(C1)**, we have the following results.

Theorem 3 Let $\left|\frac{\partial\Theta_j}{\partial x_j}(\zeta(\tau_0))\right|e^{\int_0^{\tau_0}\frac{\partial F_j}{\partial x_j}(\zeta(r))dr}<1\ (j=1,2)$, $\left|\frac{\partial\Theta_3}{\partial x_3}(\zeta(\tau_0))\right|e^{\int_0^{\tau_0}\frac{\partial F_3}{\partial x_3}(\zeta(r))dr}=1$ and $z_2^*(\bar{\tau}(\alpha),\alpha)\geq 0$ (for $\alpha>0$ small enough) be satisfied. We have the following results:

a) If $B_3C_3\neq 0$ we have a bifurcation of nontrivial periodic solutions of (7)-(12) with period $\tau(\alpha)=\tau_0+\bar{\tau}(\alpha)$ starting from $X_0+\alpha Y_0+Z^*(\bar{\tau}(\alpha),\alpha)$ for all $\alpha(>0)$ small enough, moreover $\bar{\tau}(\alpha)\simeq -\dfrac{C_3}{2B_3}\alpha$. Consequently, we have a supercritical bifurcation if $B_3C_3<0$ and a subcritical cases if $B_3C_3>0$.

b) If $B_3C_3=0$ we have an undetermined cases.

Note that in the particular case $Z=(z_1,0,0)$ we have $M_2\left(\bar{\tau},\left(-\dfrac{\acute{c}_0}{\acute{a}_0}\alpha+z_1,0,\alpha\right)\right)=0$, for all $(\bar{\tau},z_1,\alpha)\in\mathbb{R}^3$. Then, equation (18) is reduced to

$$\begin{cases} M_1\left(\bar{\tau},\left(-\frac{\acute{c}_0}{\acute{a}_0}\alpha+z_1,0,\alpha\right)\right) &= 0,\\ M_3\left(\bar{\tau},\left(-\frac{\acute{c}_0}{\acute{a}_0}\alpha+z_1,0,\alpha\right)\right) &= 0.\end{cases} \tag{27}$$

We have $\frac{\partial M_1(0,(0,0,0))}{\partial z_1}=\frac{\partial M_1(0,(0,0,0))}{\partial x_1}\frac{\partial x_1}{\partial z_1}=\acute{a}_0\neq 0$. By the implicit function theorem, there exist $\delta>0$ sufficiently small and a unique continuous function Z^*, such that $Z^*(\bar{\tau},\alpha)=(z_1^*(\bar{\tau},\alpha),0,0)$, $Z^*(0,0)=(0,0,0)$ and $M_1\left(\bar{\tau},\left(-\dfrac{\acute{c}_0}{\acute{a}_0}\alpha+z_1^*(\bar{\tau},\alpha),0,\alpha\right)\right)=0$ for every $(\bar{\tau},\alpha)$ such that $0<\alpha<\delta$ and $|\bar{\tau}|<\delta$.
Then $M(\bar{\tau},\bar{X})=0$ if and only if $f_3(\bar{\tau},\alpha)=M_3\left(\bar{\tau},\left(-\dfrac{\acute{c}_0}{\acute{a}_0}\alpha+z_1^*(\bar{\tau},\alpha),0,\alpha\right)\right)=0$.
In conclusion, we have the following results.

Theorem 4 Let $\left|\frac{\partial\Theta_j}{\partial x_j}(\zeta(\tau_0))\right|e^{\int_0^{\tau_0}\frac{\partial F_j}{\partial x_j}(\zeta(r))dr}<1\ (j=1,2)$ and $\left|\frac{\partial\Theta_3}{\partial x_3}(\zeta(\tau_0))\right|e^{\int_0^{\tau_0}\frac{\partial F_3}{\partial x_3}(\zeta(r))dr}=1$ be satisfied, then we have the same results as in theorem 3.

Remark 3 In the case **(C3)** we have:
(i) If $\acute{h}_0\neq 0$, then $A_2=B_2=C_2=0$, which is an undetermined case, to study it we need to determine the higher derivatives of f_2.
(ii) If $\acute{h}_0=0$, then $\dim\ker(E)=2$, in this case the approach above can not be applied.

2.3. **Applications to the cancer model (1)-(6).** In this section we apply the results obtained above to the model (1)-(6).
By taking $x_2 = 0$ and $x_3 = 0$, the problem (1), (4) has a τ_0-periodic solution $x_1(t, (x_0, 0, 0)) = x_s(t)$, $0 < t \le \tau_0$, where

$$x_s(t) = \frac{K_1(T_1 - e^{-r_1\tau_0})}{(T_1 - e^{-r_1\tau_0}) + (1 - T_1)e^{-r_1 t}}, \tag{28}$$

with $x_0 = \dfrac{K_1(T_1 - e^{-r_1\tau_0})}{1 - e^{-r_1\tau_0}}$.
The solution x_s is defined and stable in the one dimensional space if and only if $T_1 > e^{-r_1\tau_0}$, that is

$$\tau_0 > \frac{1}{r_1}\ln\left(\frac{1}{T_1}\right). \tag{29}$$

To determine the stability of the trivial solution $\zeta = (x_s, 0, 0)$ in the three dimensional space, we must calculate $\acute{e_0}$ and $\acute{i_0}$. We have
$\acute{e_0} = 1 - (T_2 - R)T_1^{\frac{-r_2\lambda_2K_1}{r_1}} e^{(r_2 - r_2\lambda_2K_1 - m)\tau_0}$ and $\acute{i_0} = 1 - T_3T_1^{\frac{-r_3\lambda_3K_1}{r_1}} e^{(r_3 - r_3\lambda_3K_1)\tau_0}$.
In view of the fact that $\lambda_2K_1 < 1$ and $\lambda_3K_1 < 1$ (see [8]), we have

$$T_2 < T_1^{\frac{r_2\lambda_2K_1}{r_1}} + R \tag{30}$$

and

$$T_3 < T_1^{\frac{r_3\lambda_3K_1}{r_1}}. \tag{31}$$

If $\acute{e_0} > 0$ and $\acute{i_0} > 0$, then ζ is stable as an equilibrium for the full system (1)-(6). In this case, we have

$$\frac{\ln(\frac{1}{T_1})}{r_1} < \tau_0 < \frac{\ln\left(T_1^{\frac{r_2\lambda_2K_1}{r_1}}(T_2 - R)^{-1}\right)}{r_2(1 - \lambda_2K_1) - m} \text{ and } \frac{\ln(\frac{1}{T_1})}{r_1} < \tau_0 < \frac{\ln\left(T_1^{\frac{r_3\lambda_3K_1}{r_1}}T_3^{-1}\right)}{r_3(1 - \lambda_3K_1)}.$$

So

$$\frac{\ln(\frac{1}{T_1})}{r_1} < \tau_0 < \min\left(\frac{\ln\left(T_1^{\frac{r_2\lambda_2K_1}{r_1}}(T_2 - R)^{-1}\right)}{r_2(1 - \lambda_2K_1) - m}, \frac{\ln\left(T_1^{\frac{r_3\lambda_3K_1}{r_1}}T_3^{-1}\right)}{r_3(1 - \lambda_3K_1)}\right). \tag{32}$$

Using theorem 1, we deduce the following result.
Corollary 1 If (30)-(32) are satisfied, then the trivial solution $\zeta = (x_s, 0, 0)$ of (1)-(6) is exponentially stable.
If conditions (30), (31) are satisfied and

$$T_2 > T_1^{\frac{K_1(r_2\lambda_2 - r_2\lambda_3 + m\lambda_3)}{r_1(1-\lambda_3K_1)}} T_3^{\frac{r_2(1-\lambda_2K_1)-m}{r_3(1-\lambda_3K_1)}} + R, \tag{33}$$

we have $\min\left(\dfrac{\ln\left(T_1^{\frac{r_2\lambda_2K_1}{r_1}}(T_2 - R)^{-1}\right)}{r_2(1 - \lambda_2K_1) - m}, \dfrac{\ln\left(T_1^{\frac{r_3\lambda_3K_1}{r_1}}T_3^{-1}\right)}{r_3(1 - \lambda_3K_1)}\right) = \dfrac{\ln\left(T_1^{\frac{r_2\lambda_2K_1}{r_1}}(T_2 - R)^{-1}\right)}{r_2(1 - \lambda_2K_1) - m}$.
That is, the trivial solution is stable for

$$\frac{\ln(\frac{1}{T_1})}{r_1} < \tau_0 < \frac{\ln\left(T_1^{\frac{r_2\lambda_2K_1}{r_1}}(T_2 - R)^{-1}\right)}{r_2(1 - \lambda_2K_1) - m}. \tag{34}$$

If conditions (30), (31) are satisfied and

$$T_2 < T_1^{\frac{K_1(r_2\lambda_2 - r_2\lambda_3 + m\lambda_3)}{r_1(1-\lambda_3 K_1)}} T_3^{\frac{r_2(1-\lambda_2 K_1)-m}{r_3(1-\lambda_3 K_1)}} + R, \tag{35}$$

we have $\min\left(\frac{\ln\left(T_1^{\frac{r_2\lambda_2 K_1}{r_1}}(T_2-R)^{-1}\right)}{r_2(1-\lambda_2K_1)-m}, \frac{\ln\left(T_1^{\frac{r_3\lambda_3 K_1}{r_1}}T_3^{-1}\right)}{r_3(1-\lambda_3K_1)}\right) = \frac{\ln\left(T_1^{\frac{r_3\lambda_3 K_1}{r_1}}T_3^{-1}\right)}{r_3(1-\lambda_3K_1)}$.

That is, we have stability of the trivial solution for

$$\frac{\ln(\frac{1}{T_1})}{r_1} < \tau_0 < \frac{\ln\left(T_1^{\frac{r_3\lambda_3 K_1}{r_1}}T_3^{-1}\right)}{r_3(1-\lambda_3K_1)}. \tag{36}$$

Remark 4 Equality

$$\tau_0 = \frac{\ln\left(T_1^{\frac{r_2\lambda_2 K_1}{r_1}}(T_2-R)^{-1}\right)}{r_2(1-\lambda_2K_1)-m}, \tag{37}$$

corresponds to $\acute{e_0} = 0$ and equality

$$\tau_0 = \frac{\ln\left(T_1^{\frac{r_3\lambda_3 K_1}{r_1}}T_3^{-1}\right)}{r_3(1-\lambda_3K_1)}, \tag{38}$$

corresponds to $\acute{i_0} = 0$.
If (29)-(31), (33) and (37) are satisfied, we deduce that $\acute{e_0} = 0$ and $\acute{i_0} \neq 0$, so the conditions of theorem 2 are satisfied. Further, for $\lambda_2 = 0$ we have
$B_2 = -(T_2-R)\,(r_2-m)\,e^{(r_2-m)\tau_0} < 0$ and

$$C_2 = (T_2-R)\frac{r_2 e^{(r_2-m)\tau_0}}{k_2(r_2-m)}(e^{(r_2-m)\tau_0}-1)$$
$$+(T_2-R)\frac{2r_2 m e^{(r_2-m)\tau_0}}{k_2}\int_0^{\tau_0}\int_0^u \frac{e^{r_3 u}((T_1-e^{-r_1\tau_0})e^{r_1 u}+(1-T_1))^{\frac{-r_3\lambda_3K_1}{r_1}}}{e^{-(r_2-r_3-m)s}((T_1-e^{-r_1\tau_0})e^{r_1 s}+(1-T_1))^{\frac{-r_3\lambda_3K_1}{r_1}}}dsdu$$
$$+(T_2-R)\frac{2\left(\frac{-\acute{h_0}}{\acute{i_0}}\right)r_2e^{(r_2-m)\tau_0}}{k_2(1-e^{-r_1\tau_0})^{\frac{-r_3\lambda_3K_1}{r_1}}}\int_0^{\tau_0} e^{r_3 u}((T_1-e^{-r_1\tau_0})e^{r_1 u}+(1-T_1))^{\frac{-r_3\lambda_3K_1}{r_1}}du.$$

From conditions cited above, we have $\acute{i_0} > 0$ and $\acute{h_0} < 0$, then $C_2 > 0$, therefore $B_2C_2 < 0$. From theorem 2 we have
Corollary 2 If conditions (29)-(31), (33) and (37) hold, then there exists $\epsilon_0 > 0$, such that for all $|\lambda_2| < \epsilon_0$, the problem (1)-(6) has a nontrivial periodic solutions. More specifically, there exists $\beta > 0$, such that for all $0 < \alpha < \beta$, we have a nontrivial $(\tau_0 + \bar{\tau}(\alpha))$-periodic solution

$$\Phi\left(.,\left(x_0 + \left(\frac{\acute{c_0}\acute{h_0}}{\acute{a_0}\acute{i_0}} - \frac{\acute{b_0}}{\acute{a_0}}\right)\alpha + z_1^*(\bar{\tau}(\alpha),\alpha), \alpha, -\frac{\acute{h_0}}{\acute{i_0}}\alpha + z_3^*(\bar{\tau}(\alpha),\alpha)\right)\right).$$

If (29)-(31), (35) and (38) are satisfied, we deduce that $\acute{e_0} \neq 0$ and $\acute{i_0} = 0$, so the conditions of theorem 4 are satisfied.
Further, for $\lambda_3 = 0$, we have
$B_3 = -r_3T_3e^{r_3\tau_0} < 0$ and $C_3 = 2K_3^{-1}T_3e^{r_3\tau_0}(e^{r_3\tau_0}-1) > 0$, therefore $B_3C_3 < 0$.
From theorem 4 we have
Corollary 3 If conditions (29)-(31), (35) and (38) hold, then there exists $\epsilon_0 > 0$, such that for all $|\lambda_3| < \epsilon_0$, the problem (1)-(6) has a nontrivial periodic solutions.

More specifically, there exists $\beta > 0$, such that for all $0 < \alpha < \beta$, we have a nontrivial $(\tau_0+\bar{\tau}(\alpha))$-periodic solution $\Phi\left(.,\left(x_0+\left(\frac{-\acute{c}_0}{\acute{a}_0}\right)\alpha+z_1^*(\bar{\tau}(\alpha),\alpha),0,\alpha\right)\right)$.

3. Conclusion

In this work, we have studied a nonlinear mathematical model describing evolution of cell population constituted by three kinds of cells (normal cells, sensitive tumor cells and resistant tumor cells) under periodic pulsed chemotherapeutic treatment. We have found sufficient conditions for exponential stability of trivial periodic solutions corresponding to eradication of the tumor. We have studied conditions of bifurcation of nontrivial periodic solutions which corresponds to the onset of the tumor, that is the disease is eradicated but it is still viable, and it reappears for small perturbation on the treatment period τ. Bifurcation of nontrivial periodic solutions are studied in (**C1** and **C2**) corresponding to weak drug destruction rates of sensitive tumor cells, resistant tumor cells and the both tumor cells, respectively, that is the drug action on the tumor cells is not very efficient. Note that the case **(C3)** needs a more specific study of the higher derivatives of terms describing the evolution of the population and chemotherapy functions, it should be interesting to consider a dependence with respect to the drug dose treatment in order to study the perturbation in both parameters (dose treatment and period of administration), also a study in case of many drugs should be interesting these works are in preparation. In this work we consider an impulsive differential equations, it should be interesting and more realistic to consider a functional dependence like constant delays in the differential equations.

4. Appendix

4.1. **First derivatives of Φ.** From (2.11), for all $t \in [0,\tau]$, we have

$$\frac{d}{dt}\begin{pmatrix} \frac{\partial\Phi_1(t,X_0)}{\partial x_1} & \frac{\partial\Phi_1(t,X_0)}{\partial x_2} & \frac{\partial\Phi_1(t,X_0)}{\partial x_3} \\ \frac{\partial\Phi_2(t,X_0)}{\partial x_1} & \frac{\partial\Phi_2(t,X_0)}{\partial x_2} & \frac{\partial\Phi_2(t,X_0)}{\partial x_3} \\ \frac{\partial\Phi_3(t,X_0)}{\partial x_1} & \frac{\partial\Phi_3(t,X_0)}{\partial x_2} & \frac{\partial\Phi_3(t,X_0)}{\partial x_3} \end{pmatrix} = \begin{pmatrix} \frac{\partial F_1(\zeta(t))}{\partial x_1} & \frac{\partial F_1(\zeta(t))}{\partial x_2} & \frac{\partial F_1(\zeta(t))}{\partial x_3} \\ 0 & \frac{\partial F_2(\zeta(t))}{\partial x_2} & 0 \\ 0 & \frac{\partial F_3(\zeta(t))}{\partial x_2} & \frac{\partial F_3(\zeta(t))}{\partial x_3} \end{pmatrix}$$
$$\times \begin{pmatrix} \frac{\partial\Phi_1(t,X_0)}{\partial x_1} & \frac{\partial\Phi_1(t,X_0)}{\partial x_2} & \frac{\partial\Phi_1(t,X_0)}{\partial x_3} \\ \frac{\partial\Phi_2(t,X_0)}{\partial x_1} & \frac{\partial\Phi_2(t,X_0)}{\partial x_2} & \frac{\partial\Phi_2(t,X_0)}{\partial x_3} \\ \frac{\partial\Phi_3(t,X_0)}{\partial x_1} & \frac{\partial\Phi_3(t,X_0)}{\partial x_2} & \frac{\partial\Phi_3(t,X_0)}{\partial x_3} \end{pmatrix},$$

with the initial condition $D_X(\Phi(0,X_0)) = I_{\mathbb{R}^3}$. Then we obtain

$$\frac{\partial\Phi_2(t,X_0)}{\partial x_1} = 0, \tag{39}$$

$$\frac{\partial\Phi_2(t,X_0)}{\partial x_2} = \exp\left(\int_0^t \frac{\partial F_2(\zeta(r))}{\partial x_2}dr\right), \tag{40}$$

$$\frac{\partial\Phi_2(t,X_0)}{\partial x_3} = 0, \tag{41}$$

$$\frac{\partial\Phi_3(t,X_0)}{\partial x_1} = 0, \tag{42}$$

$$\frac{\partial\Phi_3(t,X_0)}{\partial x_2} = \int_0^t \exp\left(\int_u^t \frac{\partial F_3(\zeta(r))}{\partial x_3}dr\right)\left(\frac{\partial F_3(\zeta(u))}{\partial x_2}\right)\exp\left(\int_0^u \frac{\partial F_2(\zeta(r))}{\partial x_2}dr\right)du, \tag{43}$$

$$\frac{\partial\Phi_3(t,X_0)}{\partial x_3} = \exp\left(\int_0^t \frac{\partial F_3(\zeta(r))}{\partial x_3}dr\right), \tag{44}$$

$$\frac{\partial\Phi_1(t,X_0)}{\partial x_1} = \exp\left(\int_0^t \frac{\partial F_1(\zeta(r))}{\partial x_1}dr\right),$$

$$\frac{\partial\Phi_1(t,X_0)}{\partial x_2} = \int_0^t \exp\left(\int_s^t \frac{\partial F_1(\zeta(r))}{\partial x_1}dr\right)\left\{\left(\frac{\partial F_1(\zeta(s))}{\partial x_2}\right)\exp\left(\int_0^s \frac{\partial F_2(\zeta(r))}{\partial x_2}dr\right)\right.$$

$$\left.+\left(\frac{\partial F_1(\zeta(s))}{\partial x_3}\right)\int_0^s \exp\left(\int_u^s \frac{\partial F_3(\zeta(r))}{\partial x_3}dr\right)\left(\frac{\partial F_3(\zeta(u))}{\partial x_2}\right)\exp\left(\int_0^u \frac{\partial F_2(\zeta(r))}{\partial x_2}dr\right)du\right\}ds$$

and

$$\frac{\partial\Phi_1(t,X_0)}{\partial x_3} = \int_0^t \exp\left(\int_u^t \frac{\partial F_1(\zeta(r))}{\partial x_1}dr\right)\left(\frac{\partial F_1(\zeta(u))}{\partial x_3}\right)\exp\left(\int_0^u \frac{\partial F_3(\zeta(r))}{\partial x_3}dr\right)du \qquad (45)$$

for all $0 \le t \le \tau$.

From (2.14), we have

$$\begin{pmatrix} \acute{a} & \acute{b} & \acute{c} \\ \acute{d} & \acute{e} & \acute{f} \\ \acute{g} & \acute{h} & \acute{i} \end{pmatrix} = \begin{pmatrix} 1-\sum_{i=1}^{3}\frac{\partial\Theta_1}{\partial x_i}\frac{\partial\Phi_i}{\partial x_1} & -\sum_{i=1}^{3}\frac{\partial\Theta_1}{\partial x_i}\frac{\partial\Phi_i}{\partial x_2} & -\sum_{i=1}^{3}\frac{\partial\Theta_1}{\partial x_i}\frac{\partial\Phi_i}{\partial x_3} \\ -\sum_{i=1}^{3}\frac{\partial\Theta_2}{\partial x_i}\frac{\partial\Phi_i}{\partial x_1} & 1-\sum_{i=1}^{3}\frac{\partial\Theta_2}{\partial x_i}\frac{\partial\Phi_i}{\partial x_2} & -\sum_{i=1}^{3}\frac{\partial\Theta_2}{\partial x_i}\frac{\partial\Phi_i}{\partial x_3} \\ -\sum_{i=1}^{3}\frac{\partial\Theta_3}{\partial x_i}\frac{\partial\Phi_i}{\partial x_1} & -\sum_{i=1}^{3}\frac{\partial\Theta_3}{\partial x_i}\frac{\partial\Phi_i}{\partial x_2} & 1-\sum_{i=1}^{3}\frac{\partial\Theta_3}{\partial x_i}\frac{\partial\Phi_i}{\partial x_3} \end{pmatrix}\left(\tau_0+\bar{\tau}, X_0+\bar{X}\right).$$

For $\left(\bar{\tau},\bar{X}\right) = (0,0)$, we have

$$\begin{pmatrix} \acute{a}_0 & \acute{b}_0 & \acute{c}_0 \\ \acute{d}_0 & \acute{e}_0 & \acute{f}_0 \\ \acute{g}_0 & \acute{h}_0 & \acute{i}_0 \end{pmatrix} = \begin{pmatrix} 1-\frac{\partial\Theta_1}{\partial x_1}\frac{\partial\Phi_1}{\partial x_1} & -\sum_{i=1}^{3}\frac{\partial\Theta_1}{\partial x_i}\frac{\partial\Phi_i}{\partial x_2} & -\frac{\partial\Theta_1}{\partial x_1}\frac{\partial\Phi_1}{\partial x_3}-\frac{\partial\Theta_1}{\partial x_3}\frac{\partial\Phi_3}{\partial x_3} \\ 0 & 1-\frac{\partial\Theta_2}{\partial x_2}\frac{\partial\Phi_2}{\partial x_2} & 0 \\ 0 & -\sum_{i=2}^{3}\frac{\partial\Theta_3}{\partial x_i}\frac{\partial\Phi_i}{\partial x_2} & 1-\frac{\partial\Theta_3}{\partial x_3}\frac{\partial\Phi_3}{\partial x_3} \end{pmatrix}(\tau_0, X_0).$$

4.2. **First derivatives of Z^*.**

(C1) $\acute{e}_0 = 0$ and $\acute{i}_0 \neq 0$.

Let $\eta(\bar{\tau}) = \tau_0 + \bar{\tau}$, $\eta_1(\bar{\tau},\alpha) = x_0 + \left(\frac{\acute{c}_0\acute{h}_0 - \acute{b}_0\acute{i}_0}{\acute{a}_0\acute{i}_0}\right)\alpha + z_1^*(\bar{\tau},\alpha)$, $\eta_2(\bar{\tau},\alpha) = \alpha$ and $\eta_3(\bar{\tau},\alpha) = -\frac{\alpha\acute{h}_0}{\acute{i}_0} + z_3^*(\bar{\tau},\alpha)$.

From (2.16) and (2.17) we have

$$\begin{cases} \frac{\partial M_1}{\partial\bar{\tau}}(0,0) = 0, \\ \frac{\partial M_3}{\partial\bar{\tau}}(0,0) = 0, \end{cases}$$

then

$$\begin{cases} \frac{\partial}{\partial\bar{\tau}}(\eta_1 - \Theta_1\circ\Phi(\eta,\eta_1,\eta_2,\eta_3))(0,0) = 0, \\ \frac{\partial}{\partial\bar{\tau}}(\eta_3 - \Theta_3\circ\Phi(\eta,\eta_1,\eta_2,\eta_3))(0,0) = 0. \end{cases}$$

Therefore

$$\begin{cases} \frac{\partial z_1^*(0,0)}{\partial\bar{\tau}} - \sum_{i=1}^{3}\frac{\partial\Theta_1(\Phi(\tau_0,X_0))}{\partial x_i}\left(\frac{\partial\Phi_i(\tau_0,X_0)}{\partial\bar{\tau}} + \frac{\partial\Phi_i(\tau_0,X_0)}{\partial x_1}\frac{\partial z_1^*(0,0)}{\partial\bar{\tau}} + \frac{\partial\Phi_i(\tau_0,X_0)}{\partial x_3}\frac{\partial z_3^*(0,0)}{\partial\bar{\tau}}\right) = 0, \\ \frac{\partial z_3^*(0,0)}{\partial\bar{\tau}} - \sum_{i=1}^{3}\frac{\partial\Theta_3(\Phi(\tau_0,X_0))}{\partial x_i}\left(\frac{\partial\Phi_i(\tau_0,X_0)}{\partial\bar{\tau}} + \frac{\partial\Phi_i(\tau_0,X_0)}{\partial x_1}\frac{\partial z_1^*(0,0)}{\partial\bar{\tau}} + \frac{\partial\Phi_i(\tau_0,X_0)}{\partial x_3}\frac{\partial z_3^*(0,0)}{\partial\bar{\tau}}\right) = 0. \end{cases}$$

Since $\frac{\partial\Phi_2(\tau_0,X_0)}{\partial x_1} = \frac{\partial\Phi_2(\tau_0,X_0)}{\partial x_3} = \frac{\partial\Phi_3(\tau_0,X_0)}{\partial x_1} = 0$, $\frac{\partial\Phi_2(\tau_0,X_0)}{\partial\bar{\tau}} = \frac{\partial\Phi_3(\tau_0,X_0)}{\partial\bar{\tau}} = 0$ and $\frac{\partial\Theta_3(\Phi(\tau_0,X_0))}{\partial x_1} = 0$, we obtain

$$\begin{cases} \left(1 - \frac{\partial\Theta_1(\Phi(\tau_0,X_0))}{\partial x_1}\frac{\partial\Phi_1(\tau_0,X_0)}{\partial x_1}\right)\frac{\partial z_1^*(0,0)}{\partial\bar{\tau}} - \sum_{i\neq 2}\frac{\partial\Theta_1(\Phi(\tau_0,X_0))}{\partial x_i}\frac{\partial\Phi_i(\tau_0,X_0)}{\partial x_3}\frac{\partial z_3^*(0,0)}{\partial\bar{\tau}} \\ \qquad\qquad = \frac{\partial\Theta_1(\Phi(\tau_0,X_0))}{\partial x_1}\frac{\partial\Phi_1(\tau_0,X_0)}{\partial\bar{\tau}}, \\ \left(1 - \frac{\partial\Theta_3(\Phi(\tau_0,X_0))}{\partial x_3}\frac{\partial\Phi_3(\tau_0,X_0)}{\partial x_3}\right)\frac{\partial z_3^*(0,0)}{\partial\bar{\tau}} = 0. \end{cases}$$

So

$$\begin{cases} \acute{a}_0\frac{\partial z_1^*(0,0)}{\partial\bar{\tau}} + \acute{c}_0\frac{\partial z_3^*(0,0)}{\partial\bar{\tau}} = \frac{\partial\Theta_1(\Phi(\tau_0,X_0))}{\partial x_1}\frac{\partial\Phi_1(\tau_0,X_0)}{\partial\bar{\tau}}, \\ \acute{i}_0\frac{\partial z_3^*(0,0)}{\partial\bar{\tau}} = 0, \end{cases}$$

that is

$$\begin{cases} \frac{\partial z_1^*(0,0)}{\partial\bar{\tau}} = \frac{1}{\acute{a}_0}\frac{\partial\Theta_1(\Phi(\tau_0,X_0))}{\partial x_1}\frac{\partial\Phi_1(\tau_0,X_0)}{\partial\bar{\tau}}, \\ \frac{\partial z_3^*(0,0)}{\partial\bar{\tau}} = 0. \end{cases} \tag{46}$$

In the same way as above, we obtain

$$\begin{cases} \frac{\partial}{\partial\alpha}(\eta_1 - \Theta_1\circ\Phi(\eta,\eta_1,\eta_2,\eta_3))(0,0) = 0, \\ \frac{\partial}{\partial\alpha}(\eta_3 - \Theta_3\circ\Phi(\eta,\eta_1,\eta_2,\eta_3))(0,0) = 0. \end{cases}$$

Therefore

$$\begin{cases} \left(\frac{\acute{c}_0\acute{h}_0 - \acute{b}_0\acute{i}_0}{\acute{a}_0\acute{i}_0} + \frac{\partial z_1^*(0,0)}{\partial\alpha}\right) - \sum_{i=1}^{3}\frac{\partial\Theta_1(\Phi(\tau_0,X_0))}{\partial x_i}\left\{\frac{\partial\Phi_i(\tau_0,X_0)}{\partial x_1}\left(\frac{\acute{c}_0\acute{h}_0 - \acute{b}_0\acute{i}_0}{\acute{a}_0\acute{i}_0} + \frac{\partial z_1^*(0,0)}{\partial\alpha}\right)\right. \\ \qquad\left. + \frac{\partial\Phi_i(\tau_0,X_0)}{\partial x_2} + \frac{\partial\Phi_i(\tau_0,X_0)}{\partial x_3}\left(\frac{-\acute{h}_0}{\acute{i}_0} + \frac{\partial z_3^*}{\partial\alpha}\right)\right\} = 0, \\ \left(\frac{-\acute{h}_0}{\acute{i}_0} + \frac{\partial z_3^*(0,0)}{\partial\alpha}\right) - \sum_{i=1}^{3}\frac{\partial\Theta_3(\Phi(\tau_0,X_0))}{\partial x_i}\left\{\frac{\partial\Phi_i(\tau_0,X_0)}{\partial x_1}\left(\frac{\acute{c}_0\acute{h}_0 - \acute{b}_0\acute{i}_0}{\acute{a}_0\acute{i}_0} + \frac{\partial z_1^*(0,0)}{\partial\alpha}\right)\right. \\ \qquad\left. + \frac{\partial\Phi_i(\tau_0,X_0)}{\partial x_2} + \frac{\partial\Phi_i(\tau_0,X_0)}{\partial x_3}\left(\frac{-\acute{h}_0}{\acute{i}_0} + \frac{\partial z_3^*(0,0)}{\partial\alpha}\right)\right\} = 0. \end{cases}$$

Since $\frac{\partial\Phi_2(\tau_0,X_0)}{\partial x_1} = \frac{\partial\Phi_2(\tau_0,X_0)}{\partial x_3} = \frac{\partial\Phi_3(\tau_0,X_0)}{\partial x_1} = 0$ and $\frac{\partial\Theta_3(\Phi(\tau_0,X_0))}{\partial x_1} = 0$, we obtain

$$\begin{cases} \left(1 - \frac{\partial\Theta_1(\Phi(\tau_0,X_0))}{\partial x_1}\frac{\partial\Phi_1(\tau_0,X_0)}{\partial x_1}\right)\frac{\partial z_1^*(0,0)}{\partial\alpha} - \sum_{i\neq 2}\frac{\partial\Theta_1(\Phi(\tau_0,X_0))}{\partial x_i}\frac{\partial\Phi_i(\tau_0,X_0)}{\partial x_3}\frac{\partial z_3^*(0,0)}{\partial\alpha} = \\ -\left(1 - \frac{\partial\Theta_1(\Phi(\tau_0,X_0))}{\partial x_1}\frac{\partial\Phi_1(\tau_0,X_0)}{\partial x_1}\right)\left(\frac{\acute{c}_0\acute{h}_0 - \acute{b}_0\acute{i}_0}{\acute{a}_0\acute{i}_0}\right) + \sum_{i\neq 2}\frac{\partial\Theta_1(\Phi((\tau_0,X_0))}{\partial x_i}\frac{\partial\Phi_i(\tau_0,X_0)}{\partial x_3}\left(\frac{-\acute{h}_0}{\acute{i}_0}\right) \\ \qquad + \sum_{i=1}^{3}\frac{\partial\Theta_1(\Phi(\tau_0,X_0))}{\partial x_i}\frac{\partial\Phi_i(\tau_0,X_0)}{\partial x_2}, \\ \left(1 - \frac{\partial\Theta_3(\Phi(\tau_0,X_0))}{\partial x_3}\frac{\partial\Phi_3(\tau_0,X_0)}{\partial x_3}\right)\frac{\partial z_3^*(0,0)}{\partial\alpha} = -\left(1 - \frac{\partial\Theta_3(\Phi(\tau_0,X_0))}{\partial x_3}\frac{\partial\Phi_3(\tau_0,X_0)}{\partial x_3}\right)\left(\frac{-\acute{h}_0}{\acute{i}_0}\right) \\ \qquad + \sum_{i=2}^{3}\frac{\partial\Theta_3(\Phi(\tau_0,X_0))}{\partial x_i}\frac{\partial\Phi_i(\tau_0,X_0)}{\partial x_2}. \end{cases}$$

So

$$\begin{cases} \acute{a}_0\frac{\partial z_1^*(0,0)}{\partial\alpha} + \acute{c}_0\frac{\partial z_3^*(0,0)}{\partial\alpha} = 0, \\ \acute{i}_0\frac{\partial z_3^*(0,0)}{\partial\alpha} = 0, \end{cases}$$

that is

$$\begin{cases} \frac{\partial z_1^*(0,0)}{\partial\alpha} = 0, \\ \frac{\partial z_3^*(0,0)}{\partial\alpha} = 0. \end{cases} \tag{47}$$

(C2) $\acute{e}_0 \neq 0$ and $\acute{i}_0 = 0$.
Let $\eta(\bar{\tau}) = \tau_0 + \bar{\tau}$, $\eta_1(\bar{\tau}, \alpha) = x_0 - \frac{\acute{c}_0}{\acute{a}_0}\alpha + z_1^*(\bar{\tau}, \alpha)$, $\eta_2(\bar{\tau}, \alpha) = z_2^*(\bar{\tau}, \alpha)$ and $\eta_3(\bar{\tau}, \alpha) = \alpha$.
From (2.19) and (2.20) we have

$$\begin{cases} \frac{\partial M_1}{\partial \bar{\tau}}(0,0) = 0, \\ \frac{\partial M_2}{\partial \bar{\tau}}(0,0) = 0, \end{cases}$$

In the same way as above, we obtain

$$\begin{cases} \frac{\partial z_1^*(0,0)}{\partial \bar{\tau}} = \frac{1}{\acute{a}_0} \frac{\partial \Theta_1(\Phi(\tau_0, X_0))}{\partial x_1} \frac{\partial \Phi_1(\tau_0, X_0)}{\partial \bar{\tau}}, \\ \frac{\partial z_2^*(0,0)}{\partial \bar{\tau}} = 0. \end{cases} \tag{48}$$

and

$$\begin{cases} \frac{\partial z_1^*(0,0)}{\partial \alpha} = 0, \\ \frac{\partial z_2^*(0,0)}{\partial \alpha} = 0. \end{cases} \tag{49}$$

4.3. **First derivatives of f_i.**
(C1) $\acute{e}_0 = 0$ and $\acute{i}_0 \neq 0$.
We have

$$\begin{aligned} \frac{\partial f_2}{\partial \bar{\tau}} &= \frac{\partial}{\partial \bar{\tau}}(\eta_2 - \Theta_2 \circ \Phi(\eta, \eta_1, \eta_2, \eta_3)) \\ &= -\sum_{i=1}^{3} \frac{\partial \Theta_2}{\partial x_i} \left(\frac{\partial \Phi_i(\eta, \eta_1, \eta_2, \eta_3)}{\partial \bar{\tau}} + \frac{\partial \Phi_i(\eta, \eta_1, \eta_2, \eta_3)}{\partial x_1} \frac{\partial z_1^*}{\partial \bar{\tau}} + \frac{\partial \Phi_i(\eta, \eta_1, \eta_2, \eta_3)}{\partial x_3} \frac{\partial z_3^*}{\partial \bar{\tau}} \right). \end{aligned}$$

Since $\frac{\partial \Phi_2(\tau_0, X_0)}{\partial x_1} = \frac{\partial \Phi_2(\tau_0, X_0)}{\partial x_3} = \frac{\partial \Phi_2(\tau_0, X_0)}{\partial \bar{\tau}} = 0$ and $\frac{\partial \Theta_2(\Phi(\tau_0, X_0))}{\partial x_1} = \frac{\partial \Theta_2(\Phi(\tau_0, X_0))}{\partial x_3} = 0$, we obtain $\frac{\partial f(0,0)}{\partial \bar{\tau}} = 0$. Moreover,

$$\begin{aligned} \frac{\partial f_2}{\partial \alpha} &= \frac{\partial}{\partial \alpha}(\eta_2 - \Theta_2 \circ \Phi(\eta, \eta_1, \eta_2, \eta_3)) \\ &= 1 - \sum_{i=1}^{3} \frac{\partial \Theta_2}{\partial x_i} \left\{ \frac{\partial \Phi_i(\eta, \eta_1, \eta_2, \eta_3)}{\partial x_1} \left(\frac{\acute{c}_0 \acute{h}_0 - \acute{b}_0 \acute{i}_0}{\acute{a}_0 \acute{i}_0} + \frac{\partial z_1^*}{\partial \alpha} \right) + \frac{\partial \Phi_i(\eta, \eta_1, \eta_2, \eta_3)}{\partial x_2} \right. \\ &\qquad \left. + \frac{\partial \Phi_i(\eta, \eta_1, \eta_2, \eta_3)}{\partial x_3} \left(\frac{-\acute{h}_0}{\acute{i}_0} + \frac{\partial z_3^*}{\partial \alpha} \right) \right\}. \end{aligned}$$

Since $\frac{\partial \Theta_2(\Phi(\tau_0, X_0))}{\partial x_1} = \frac{\partial \Theta_2(\Phi(\tau_0, X_0))}{\partial x_3} = 0$, $\frac{\partial \Phi_2(\tau_0, X_0)}{\partial x_1} = \frac{\partial \Phi_2(\tau_0, X_0)}{\partial x_3} = 0$ and
$1 - \frac{\partial \Theta_2(\Phi(\tau_0, X_0))}{\partial x_2} \frac{\partial \Phi_2(\tau_0, X_0)}{\partial x_2} = \acute{e}_0 = 0$, we obtain $\frac{\partial f_2(0,0)}{\partial \alpha} = 0$. Therefore $Df_2(0,0) = (0,0)$.
(C2) $\acute{e}_0 \neq 0$ and $\acute{i}_0 = 0$.
We have

$$\begin{aligned} \frac{\partial f_3}{\partial \bar{\tau}} &= \frac{\partial}{\partial \bar{\tau}}(\eta_3 - \Theta_3 \circ \Phi(\eta, \eta_1, \eta_2, \eta_3)) \\ &= -\sum_{i=1}^{3} \frac{\partial \Theta_3}{\partial x_i} \left(\frac{\partial \Phi_i(\eta, \eta_1, \eta_2, \eta_3)}{\partial \bar{\tau}} + \frac{\partial \Phi_i(\eta, \eta_1, \eta_2, \eta_3)}{\partial x_1} \frac{\partial z_1^*}{\partial \bar{\tau}} + \frac{\partial \Phi_i(\eta, \eta_1, \eta_2, \eta_3)}{\partial x_2} \frac{\partial z_2^*}{\partial \bar{\tau}} \right). \end{aligned}$$

We have $\frac{\partial \Theta_3(\Phi(\tau_0, X_0))}{\partial x_1} = \frac{\partial \Phi_2(\tau_0, X_0)}{\partial x_1} = \frac{\partial \Phi_3(\tau_0, X_0)}{\partial x_1} = 0$ and $\frac{\partial \Phi_2(\tau_0, X_0)}{\partial \bar{\tau}} = \frac{\partial \Phi_3(\tau_0, X_0)}{\partial \bar{\tau}} = 0$.

From (48), we have $\frac{\partial z_2^*(0,0)}{\partial \bar\tau}=0$, then $\frac{\partial f_3(0,0)}{\partial \bar\tau}=0$. Moreover

$$\begin{aligned}\frac{\partial f_3}{\partial \alpha} &= \frac{\partial}{\partial \alpha}(\eta_3-\Theta_3\circ\Phi(\eta,\eta_1,\eta_2,\eta_3))\\ &= 1-\sum_{i=1}^{3}\frac{\partial\Theta_3}{\partial x_i}\left\{\frac{\partial\Phi_i(\eta,\eta_1,\eta_2,\eta_3)}{\partial x_1}\left(\frac{-c_0'}{a_0'}+\frac{\partial z_1^*}{\partial\alpha}\right)+\frac{\partial\Phi_i(\eta,\eta_1,\eta_2,\eta_3)}{\partial x_2}\left(\frac{\partial z_2^*}{\partial\alpha}\right)\right.\\ &\qquad\left.+\frac{\partial\Phi_i(\eta,\eta_1,\eta_2,\eta_3)}{\partial x_3}\right\}.\end{aligned}$$

We have $\frac{\partial\Phi_2(\tau_0,X_0)}{\partial x_1}=\frac{\partial\Phi_2(\tau_0,X_0)}{\partial x_3}=\frac{\partial\Phi_3(\tau_0,X_0)}{\partial x_1}=0$, $\frac{\partial\Theta_3(\Phi(\tau_0,X_0))}{\partial x_1}=0$ and
$1-\frac{\partial\Theta_3(\Phi(\tau_0,X_0))}{\partial x_3}\frac{\partial\Phi_3(\tau_0,X_0)}{\partial x_3}=i_0'=0$.
From (49), we have $\frac{\partial z_2^*}{\partial\alpha}(0,0)=0$, then $\frac{\partial f_3(0,0)}{\partial\alpha}=0$. Therefore $Df_3(0,0)=(0,0)$.

4.4. **Second derivatives of f_i.**

Let $A_i=\frac{\partial^2 f_i(0,0)}{\partial\bar\tau^2}$, $B_i=\frac{\partial^2 f_i(0,0)}{\partial\bar\tau\partial\alpha}$ and $C_i=\frac{\partial^2 f_i(0,0)}{\partial\alpha^2}$.
(C1) $e_0'=0$ and $i_0'\neq 0$.
Calculation of A_2.
We have $\frac{\partial^2 f_2}{\partial\bar\tau^2}=\frac{\partial^2}{\partial\bar\tau^2}(\eta_2-\Theta_2\circ\Phi(\eta,\eta_1,\eta_2,\eta_3))$, then

$$\begin{aligned}\frac{\partial^2 f_2}{\partial\bar\tau^2} &= -\sum_{j=1}^{3}\sum_{i=1}^{3}\frac{\partial^2\Theta_2}{\partial x_i\partial x_j}\left(\frac{\partial\Phi_i(\eta,\eta_1,\eta_2,\eta_3)}{\partial\bar\tau}+\frac{\partial\Phi_i(\eta,\eta_1,\eta_2,\eta_3)}{\partial x_1}\frac{\partial z_1^*}{\partial\bar\tau}+\frac{\partial\Phi_i(\eta,\eta_1,\eta_2,\eta_3)}{\partial x_3}\frac{\partial z_3^*}{\partial\bar\tau}\right)\\ &\times\left(\frac{\partial\Phi_j(\eta,\eta_1,\eta_2,\eta_3)}{\partial\bar\tau}+\frac{\partial\Phi_j(\eta,\eta_1,\eta_2,\eta_3)}{\partial x_1}\frac{\partial z_1^*}{\partial\bar\tau}+\frac{\partial\Phi_j(\eta,\eta_1,\eta_2,\eta_3)}{\partial x_3}\frac{\partial z_3^*}{\partial\bar\tau}\right)\\ &-\sum_{i=1}^{3}\frac{\partial\Theta_2}{\partial x_i}\left\{\frac{\partial^2\Phi_i(\eta,\eta_1,\eta_2,\eta_3)}{\partial\bar\tau^2}+2\frac{\partial^2\Phi_i(\eta,\eta_1,\eta_2,\eta_3)}{\partial\bar\tau\partial x_1}\frac{\partial z_1^*}{\partial\bar\tau}+2\frac{\partial^2\Phi_i(\eta,\eta_1,\eta_2,\eta_3)}{\partial\bar\tau\partial x_3}\frac{\partial z_3^*}{\partial\bar\tau}\right.\\ &+\frac{\partial^2\Phi_i(\eta,\eta_1,\eta_2,\eta_3)}{\partial x_1^2}\left(\frac{\partial z_1^*}{\partial\bar\tau}\right)^2+2\frac{\partial^2\Phi_i(\eta,\eta_1,\eta_2,\eta_3)}{\partial x_1\partial x_3}\frac{\partial z_1^*}{\partial\bar\tau}\frac{\partial z_3^*}{\partial\bar\tau}+\frac{\partial\Phi_i(\eta,\eta_1,\eta_2,\eta_3)}{\partial x_1}\frac{\partial^2 z_1^*}{\partial\bar\tau^2}\\ &\left.+\frac{\partial^2\Phi_i(\eta,\eta_1,\eta_2,\eta_3)}{\partial x_3^2}\left(\frac{\partial z_3^*}{\partial\bar\tau}\right)^2+\frac{\partial\Phi_i(\eta,\eta_1,\eta_2,\eta_3)}{\partial x_3}\frac{\partial^2 z_3^*}{\partial\bar\tau^2}\right\}.\end{aligned}$$

We have $\frac{\partial^2\Theta_2(\Phi(\tau_0,X_0))}{\partial x_1^2}=\frac{\partial\Theta_2(\Phi(\tau_0,X_0))}{\partial x_1}=\frac{\partial\Theta_2(\Phi(\tau_0,X_0))}{\partial x_3}=0$, $\frac{\partial\Phi_2(\tau_0,X_0)}{\partial x_1}=\frac{\partial\Phi_3(\tau_0,X_0)}{\partial x_1}=\frac{\partial\Phi_2(\tau_0,X_0)}{\partial x_3}=0$ and $\frac{\partial^2\Phi_2(\tau_0,X_0)}{\partial\bar\tau^2}=\frac{\partial\Phi_2(\tau_0,X_0)}{\partial\bar\tau}=\frac{\partial\Phi_3(\tau_0,X_0)}{\partial\bar\tau}=0$.
From (39) and (46), we have $\frac{\partial^2\Phi_2(\tau_0,X_0)}{\partial x_1^2}=\frac{\partial^2\Phi_2(\tau_0,X_0)}{\partial\bar\tau\partial x_1}=0$ and $\frac{\partial z_3^*(0,0)}{\partial\bar\tau}=0$, then $A_2=0$.
Calculation of C_2.
We have $\frac{\partial^2 f_2}{\partial\alpha^2}=\frac{\partial^2}{\partial\alpha^2}(\eta_2-\Theta_2\circ\Phi(\eta,\eta_1,\eta_2,\eta_3))$, then

$$\begin{aligned}\frac{\partial^2 f_2}{\partial\alpha^2} &= -\sum_{j=1}^{3}\sum_{i=1}^{3}\frac{\partial^2\Theta_2}{\partial x_i\partial x_j}\\ &\times\left\{\frac{\partial\Phi_i(\eta,\eta_1,\eta_2,\eta_3)}{\partial x_1}\left(\frac{c_0'h_0'-b_0'i_0'}{a_0'i_0'}+\frac{\partial z_1^*}{\partial\alpha}\right)+\frac{\partial\Phi_i(\eta,\eta_1,\eta_2,\eta_3)}{\partial x_2}+\frac{\partial\Phi_i(\eta,\eta_1,\eta_2,\eta_3)}{\partial x_3}\left(\frac{-h_0'}{i_0'}+\frac{\partial z_3^*}{\partial\alpha}\right)\right\}\\ &\times\left\{\frac{\partial\Phi_j(\eta,\eta_1,\eta_2,\eta_3)}{\partial x_1}\left(\frac{c_0'h_0'-b_0'i_0'}{a_0'i_0'}+\frac{\partial z_1^*}{\partial\alpha}\right)+\frac{\partial\Phi_j(\eta,\eta_1,\eta_2,\eta_3)}{\partial x_2}+\frac{\partial\Phi_j(\eta,\eta_1,\eta_2,\eta_3)}{\partial x_3}\left(\frac{-h_0'}{i_0'}+\frac{\partial z_3^*}{\partial\alpha}\right)\right\}\\ &-\sum_{i=1}^{3}\frac{\partial\Theta_2}{\partial x_i}\left\{\frac{\partial^2\Phi_i(\eta,\eta_1,\eta_2,\eta_3)}{\partial x_1^2}\left(\frac{c_0'h_0'-b_0'i_0'}{a_0'i_0'}+\frac{\partial z_1^*}{\partial\alpha}\right)^2+2\frac{\partial^2\Phi_i(\eta,\eta_1,\eta_2,\eta_3)}{\partial x_2\partial x_1}\left(\frac{c_0'h_0'-b_0'i_0'}{a_0'i_0'}+\frac{\partial z_1^*}{\partial\alpha}\right)\right.\\ &+2\frac{\partial^2\Phi_i(\eta,\eta_1,\eta_2,\eta_3)}{\partial x_3\partial x_1}\left(\frac{-h_0'}{i_0'}+\frac{\partial z_3^*}{\partial\alpha}\right)\left(\frac{c_0'h_0'-b_0'i_0'}{a_0'i_0'}+\frac{\partial z_1^*}{\partial\alpha}\right)+\frac{\partial\Phi_i(\eta,\eta_1,\eta_2,\eta_3)}{\partial x_1}\left(\frac{\partial^2 z_1^*}{\partial\alpha^2}\right)\\ &\left.+\frac{\partial^2\Phi_i(\eta,\eta_1,\eta_2,\eta_3)}{\partial x_2^2}+2\frac{\partial^2\Phi_i(\eta,\eta_1,\eta_2,\eta_3)}{\partial x_3\partial x_2}\left(\frac{-h_0'}{i_0'}+\frac{\partial z_3^*}{\partial\alpha}\right)\frac{\partial z_2^*}{\partial\alpha}+\frac{\partial^2\Phi_i(\eta,\eta_1,\eta_2,\eta_3)}{\partial x_3^2}\left(\frac{-h_0'}{i_0'}+\frac{\partial z_3^*}{\partial\alpha}\right)^2\right\}.\end{aligned}$$

From (39) and (41), we have $\frac{\partial^2\Phi_2(\tau_0,X_0)}{\partial x_1\partial x_3} = \frac{\partial^2\Phi_2(\tau_0,X_0)}{\partial x_3^2} = 0$.
For determining C_2, we must calculate (E_1): $\frac{\partial^2\Phi_2}{\partial x_2\partial x_1}$, (E_2): $\frac{\partial^2\Phi_2}{\partial x_2^2}$ and (E_3): $\frac{\partial^2\Phi_2}{\partial x_3\partial x_2}$ at (τ_0, X_0).
The second partial derivatives of Φ_2 can be obtained from the following differential equations

$$\begin{aligned}(E_1): \frac{d}{dt}\left(\frac{\partial^2\Phi_2(t,X_0)}{\partial x_2\partial x_1}\right) &= \frac{\partial F_2(\zeta(t))}{\partial x_1}\frac{\partial^2\Phi_1(t,X_0)}{\partial x_2\partial x_1} + \frac{\partial F_2(\zeta(t))}{\partial x_2}\frac{\partial^2\Phi_2(t,X_0)}{\partial x_2\partial x_1} + \frac{\partial F_2(\zeta(t))}{\partial x_3}\frac{\partial^2\Phi_3(t,X_0)}{\partial x_2\partial x_1}\\ &+ \left(\frac{\partial^2 F_2(\zeta(t))}{\partial x_1^2}\frac{\partial\Phi_1(t,X_0)}{\partial x_2} + \frac{\partial^2 F_2(\zeta(t))}{\partial x_2\partial x_1}\frac{\partial\Phi_2(t,X_0)}{\partial x_2} + \frac{\partial^2 F_2(\zeta(t))}{\partial x_3\partial x_1}\frac{\partial\Phi_3(t,X_0)}{\partial x_2}\right)\frac{\partial\Phi_1(t,X_0)}{\partial x_1}\\ &+ \left(\frac{\partial^2 F_2(\zeta(t))}{\partial x_1\partial x_2}\frac{\partial\Phi_1(t,X_0)}{\partial x_2} + \frac{\partial^2 F_2(\zeta(t))}{\partial x_2^2}\frac{\partial\Phi_2(t,X_0)}{\partial x_2} + \frac{\partial^2 F_2(\zeta(t))}{\partial x_3\partial x_2}\frac{\partial\Phi_3(t,X_0)}{\partial x_2}\right)\frac{\partial\Phi_2(t,X_0)}{\partial x_1}\\ &+ \left(\frac{\partial^2 F_2(\zeta(t))}{\partial x_1\partial x_3}\frac{\partial\Phi_1(t,X_0)}{\partial x_2} + \frac{\partial^2 F_2(\zeta(t))}{\partial x_2\partial x_3}\frac{\partial\Phi_2(t,X_0)}{\partial x_2} + \frac{\partial^2 F_2(\zeta(t))}{\partial x_3^2}\frac{\partial\Phi_3(t,X_0)}{\partial x_2}\right)\frac{\partial\Phi_3(t,X_0)}{\partial x_1}\end{aligned}$$

with the initial condition $\frac{\partial^2\Phi_2(0,X_0)}{\partial x_2\partial x_1} = 0$, then

$$\frac{d}{dt}\left(\frac{\partial^2\Phi_2(t,X_0)}{\partial x_2\partial x_1}\right) = \frac{\partial F_2(\zeta(t))}{\partial x_2}\frac{\partial^2\Phi_2(t,X_0)}{\partial x_2\partial x_1} + \frac{\partial^2 F_2(\zeta(t))}{\partial x_2\partial x_1}\frac{\partial\Phi_2(\tau_0,X_0)}{\partial x_2}\frac{\partial\Phi_1(\tau_0,X_0)}{\partial x_1}$$

with the initial condition $\frac{\partial^2\Phi_2(0,X_0)}{\partial x_2\partial x_1} = 0$. We obtain

$$\frac{\partial^2\Phi_2(t,X_0)}{\partial x_2\partial x_1} = \int_0^t \exp\left(\int_0^t \frac{\partial F_2(\zeta(s))}{\partial x_2}ds\right)\left(\frac{\partial^2 F_2(\zeta(r))}{\partial x_2\partial x_1}\right)\exp\left(\int_0^r \frac{\partial F_1(\zeta(s))}{\partial x_1}ds\right)dr.$$

$$\begin{aligned}(E_2): \frac{d}{dt}\left(\frac{\partial^2\Phi_2(t,X_0)}{\partial x_2^2}\right) &= \frac{\partial F_2(\zeta(t))}{\partial x_1}\frac{\partial^2\Phi_1(t,X_0)}{\partial x_2^2} + \frac{\partial F_2(\zeta(t))}{\partial x_2}\frac{\partial^2\Phi_2(t,X_0)}{\partial x_2^2} + \frac{\partial F_2(\zeta(t))}{\partial x_3}\frac{\partial^2\Phi_3(t,X_0)}{\partial x_2^2}\\ &+ \left(\frac{\partial^2 F_2(\zeta(t))}{\partial x_1^2}\frac{\partial\Phi_1(t,X_0)}{\partial x_2} + \frac{\partial^2 F_2(\zeta(t))}{\partial x_2\partial x_1}\frac{\partial\Phi_2(t,X_0)}{\partial x_2} + \frac{\partial^2 F_2(\zeta(t))}{\partial x_3\partial x_1}\frac{\partial\Phi_3(t,X_0)}{\partial x_2}\right)\frac{\partial\Phi_1(t,X_0)}{\partial x_2}\\ &+ \left(\frac{\partial^2 F_2(\zeta(t))}{\partial x_1\partial x_2}\frac{\partial\Phi_1(t,X_0)}{\partial x_2} + \frac{\partial^2 F_2(\zeta(t))}{\partial x_2^2}\frac{\partial\Phi_2(t,X_0)}{\partial x_2} + \frac{\partial^2 F_2(\zeta(t))}{\partial x_3\partial x_2}\frac{\partial\Phi_3(t,X_0)}{\partial x_2}\right)\frac{\partial\Phi_2(t,X_0)}{\partial x_2}\\ &+ \left(\frac{\partial^2 F_2(\zeta(t))}{\partial x_1\partial x_3}\frac{\partial\Phi_1(t,X_0)}{\partial x_2} + \frac{\partial^2 F_2(\zeta(t))}{\partial x_2\partial x_3}\frac{\partial\Phi_2(t,X_0)}{\partial x_2} + \frac{\partial^2 F_2(\zeta(t))}{\partial x_3^2}\frac{\partial\Phi_3(t,X_0)}{\partial x_2}\right)\frac{\partial\Phi_3(t,X_0)}{\partial x_2}\end{aligned}$$

with the initial condition $\frac{\partial^2\Phi_2(0,X_0)}{\partial x_2^2} = 0$, then

$$\begin{aligned}\frac{d}{dt}\left(\frac{\partial^2\Phi_2(t,X_0)}{\partial x_2^2}\right) &= \frac{\partial F_2(\zeta(t))}{\partial x_2}\frac{\partial^2\Phi_2(t,X_0)}{\partial x_2^2} + \left\{2\frac{\partial^2 F_2(\zeta(t))}{\partial x_1\partial x_2}\frac{\partial\Phi_1(t,X_0)}{\partial x_2} + \frac{\partial^2 F_2(\zeta(t))}{\partial x_2^2}\frac{\partial\Phi_2(t,X_0)}{\partial x_2}\right.\\ &\left.\quad + 2\frac{\partial^2 F_2(\zeta(t))}{\partial x_3\partial x_2}\frac{\partial\Phi_3(t,X_0)}{\partial x_2}\right\}\frac{\partial\Phi_2(t,X_0)}{\partial x_2}\end{aligned}$$

with the initial condition $\frac{\partial^2\Phi_2(0,X_0)}{\partial x_2^2} = 0$. We obtain

$$\begin{aligned}\frac{\partial^2\Phi_2(t,X_0)}{\partial x_2^2} &= \int_0^t \exp\left(\int_0^t \frac{\partial F_2(\zeta(s))}{\partial x_2}ds\right)\left\{2\frac{\partial^2 F_2(\zeta(r))}{\partial x_2\partial x_1}\frac{\partial\Phi_1(r,X_0)}{\partial x_2} + \frac{\partial^2 F_2(\zeta(r))}{\partial x_2^2}\frac{\partial\Phi_2(r,X_0)}{\partial x_2}\right.\\ &\left.\quad +2\frac{\partial^2 F_2(\zeta(r))}{\partial x_3\partial x_2}\frac{\partial\Phi_3(r,X_0)}{\partial x_2}\right\}dr.\end{aligned}$$

$$\begin{aligned}(E_3): \frac{d}{dt}\left(\frac{\partial^2\Phi_2(t,X_0)}{\partial x_3\partial x_2}\right) &= \frac{\partial F_2(\zeta(t))}{\partial x_1}\frac{\partial^2\Phi_1(t,X_0)}{\partial x_3\partial x_2} + \frac{\partial F_2(\zeta(t))}{\partial x_2}\frac{\partial^2\Phi_2(t,X_0)}{\partial x_3\partial x_2} + \frac{\partial F_2(\zeta(t))}{\partial x_3}\frac{\partial^2\Phi_3(t,X_0)}{\partial x_3\partial x_2}\\ &+ \left(\frac{\partial^2 F_2(\zeta(t))}{\partial x_1^2}\frac{\partial\Phi_1(t,X_0)}{\partial x_3} + \frac{\partial^2 F_2(\zeta(t))}{\partial x_2\partial x_1}\frac{\partial\Phi_2(t,X_0)}{\partial x_3} + \frac{\partial^2 F_2(\zeta(t))}{\partial x_3\partial x_1}\frac{\partial\Phi_3(t,X_0)}{\partial x_3}\right)\frac{\partial\Phi_1(t,X_0)}{\partial x_2}\\ &+ \left(\frac{\partial^2 F_2(\zeta(t))}{\partial x_1\partial x_2}\frac{\partial\Phi_1(t,X_0)}{\partial x_3} + \frac{\partial^2 F_2(\zeta(t))}{\partial x_2^2}\frac{\partial\Phi_2(t,X_0)}{\partial x_3} + \frac{\partial^2 F_2(\zeta(t))}{\partial x_3\partial x_2}\frac{\partial\Phi_3(t,X_0)}{\partial x_3}\right)\frac{\partial\Phi_2(t,X_0)}{\partial x_2}\\ &+ \left(\frac{\partial^2 F_2(\zeta(t))}{\partial x_1\partial x_3}\frac{\partial\Phi_1(t,X_0)}{\partial x_3} + \frac{\partial^2 F_2(\zeta(t))}{\partial x_2\partial x_3}\frac{\partial\Phi_2(t,X_0)}{\partial x_3} + \frac{\partial^2 F_2(\zeta(t))}{\partial x_3^2}\frac{\partial\Phi_3(t,X_0)}{\partial x_3}\right)\frac{\partial\Phi_3(t,X_0)}{\partial x_2}\end{aligned}$$

with the initial condition $\frac{\partial^2\Phi_2(0,X_0)}{\partial x_3\partial x_2} = 0$, then

$$\begin{aligned}\frac{d}{dt}\left(\frac{\partial^2\Phi_2(t,X_0)}{\partial x_3\partial x_2}\right) &= \frac{\partial F_2(\zeta(t))}{\partial x_2}\frac{\partial^2\Phi_2(t,X_0)}{\partial x_3\partial x_2}\\ &+ \left(\frac{\partial^2 F_2(\zeta(t))}{\partial x_1\partial x_2}\frac{\partial\Phi_1(t,X_0)}{\partial x_3} + \frac{\partial^2 F_2(\zeta(t))}{\partial x_3\partial x_2}\frac{\partial\Phi_3(t,X_0)}{\partial x_3}\right)\frac{\partial\Phi_2(t,X_0)}{\partial x_2}\end{aligned}$$

with the initial condition $\frac{\partial^2\Phi_2(0,X_0)}{\partial x_3\partial x_2}=0$. We obtain

$$\frac{\partial^2\Phi_2(t,X_0)}{\partial x_3\partial x_2}=\int_0^t\exp\left(\int_0^t\frac{\partial F_2(\zeta(s))}{\partial x_2}ds\right)\left(\frac{\partial^2F_2(\zeta(r))}{\partial x_1\partial x_2}\frac{\partial\Phi_1(r,X_0)}{\partial x_3}+\frac{\partial^2F_2(\zeta(r))}{\partial x_3\partial x_2}\frac{\partial\Phi_3(r,X_0)}{\partial x_3}\right)dr.$$

From (47), we have $\frac{\partial z_1^*(0,0)}{\partial\alpha}=\frac{\partial z_3^*(0,0)}{\partial\alpha}=0$. Therefore

$$\begin{aligned}C_2=&-2\frac{\partial^2\Theta_2(\Phi(\tau_0,X_0))}{\partial x_2\partial x_1}\frac{\partial\Phi_2(\tau_0,X_0)}{\partial x_2}\left\{\frac{\partial\Phi_1(\tau_0,X_0)}{\partial x_1}\left(\frac{\acute{c}_0\acute{h}_0-\acute{b}_0\acute{i}_0}{\acute{a}_0\acute{i}_0}\right)+\frac{\partial\Phi_1(\tau_0,X_0)}{\partial x_2}+\frac{\partial\Phi_1(\tau_0,X_0)}{\partial x_3}\left(\frac{-\acute{h}_0}{\acute{i}_0}\right)\right\}\\&-\frac{\partial^2\Theta_2(\Phi(\tau_0,X_0))}{\partial x_2^2}\left(\frac{\partial\Phi_2(\tau_0,X_0)}{\partial x_2}\right)^2-2\frac{\partial^2\Theta_2(\Phi(\tau_0,X_0))}{\partial x_3\partial x_2}\left\{\frac{\partial\Phi_3(\tau_0,X_0)}{\partial x_2}+\frac{\partial\Phi_3(\tau_0,X_0)}{\partial x_3}\left(\frac{-\acute{h}_0}{\acute{i}_0}\right)\right\}\frac{\partial\Phi_2(\tau_0,X_0)}{\partial x_2}\\&-\frac{\partial\Theta_2(\Phi(\tau_0,X_0))}{\partial x_2}\left\{2\frac{\partial^2\Phi_2(\tau_0,X_0)}{\partial x_2\partial x_1}\left(\frac{\acute{c}_0\acute{h}_0-\acute{b}_0\acute{i}_0}{\acute{a}_0\acute{i}_0}\right)+\frac{\partial^2\Phi_2(\tau_0,X_0)}{\partial x_2^2}+2\frac{\partial^2\Phi_2(\tau_0,X_0)}{\partial x_3\partial x_2}\left(\frac{-\acute{h}_0}{\acute{i}_0}\right)\right\}.\end{aligned}$$

Calculation of B_2.
We have $\frac{\partial^2f_2}{\partial\bar{\tau}\partial\alpha}=\frac{\partial}{\partial\bar{\tau}}\left(\frac{\partial}{\partial\alpha}(\eta_2-\Theta_2\circ\Phi(\eta,\eta_1,\eta_2,\eta_3))\right)$, then

$$\begin{aligned}\frac{\partial^2f_2}{\partial\bar{\tau}\partial\alpha}=&-\sum_{j=1}^3\sum_{i=1}^3\frac{\partial^2\Theta_2}{\partial x_i\partial x_j}\left(\frac{\partial\Phi_i(\eta,\eta_1,\eta_2,\eta_3)}{\partial\bar{\tau}}+\frac{\partial\Phi_i(\eta,\eta_1,\eta_2,\eta_3)}{\partial x_1}\frac{\partial z_1^*}{\partial\bar{\tau}}+\frac{\partial\Phi_i(\eta,\eta_1,\eta_2,\eta_3)}{\partial x_3}\frac{\partial z_3^*}{\partial\bar{\tau}}\right)\\&\times\left\{\frac{\partial\Phi_j(\eta,\eta_1,\eta_2,\eta_3)}{\partial x_1}\left(\frac{\acute{c}_0\acute{h}_0-\acute{b}_0\acute{i}_0}{\acute{a}_0\acute{i}_0}+\frac{\partial z_1^*}{\partial\alpha}\right)+\frac{\partial\Phi_j(\eta,\eta_1,\eta_2,\eta_3)}{\partial x_2}+\frac{\partial\Phi_j(\eta,\eta_1,\eta_2,\eta_3)}{\partial x_3}\left(\frac{-\acute{h}_0}{\acute{i}_0}+\frac{\partial z_3^*}{\partial\alpha}\right)\right\}\\&-\sum_{i=1}^3\frac{\partial\Theta_2}{\partial x_i}\left\{\frac{\partial^2\Phi_i(\eta,\eta_1,\eta_2,\eta_3)}{\partial\bar{\tau}\partial x_1}\left(\frac{\acute{c}_0\acute{h}_0-\acute{b}_0\acute{i}_0}{\acute{a}_0\acute{i}_0}+\frac{\partial z_1^*}{\partial\alpha}\right)+\frac{\partial^2\Phi_i(\eta,\eta_1,\eta_2,\eta_3)}{\partial x_1^2}\frac{\partial z_1^*}{\partial\bar{\tau}}\left(\frac{\acute{c}_0\acute{h}_0-\acute{b}_0\acute{i}_0}{\acute{a}_0\acute{i}_0}+\frac{\partial z_1^*}{\partial\alpha}\right)\right.\\&+\frac{\partial^2\Phi_i(\eta,\eta_1,\eta_2,\eta_3)}{\partial x_3\partial x_1}\frac{\partial z_3^*}{\partial\bar{\tau}}\left(\frac{\acute{c}_0\acute{h}_0-\acute{b}_0\acute{i}_0}{\acute{a}_0\acute{i}_0}+\frac{\partial z_1^*}{\partial\alpha}\right)+\frac{\partial\Phi_i(\eta,\eta_1,\eta_2,\eta_3)}{\partial x_1}\frac{\partial^2z_1^*}{\partial\bar{\tau}\partial\alpha}+\frac{\partial^2\Phi_i(\eta,\eta_1,\eta_2,\eta_3)}{\partial\bar{\tau}\partial x_2}\\&+\frac{\partial^2\Phi_i(\eta,\eta_1,\eta_2,\eta_3)}{\partial x_1\partial x_2}\frac{\partial z_1^*}{\partial\bar{\tau}}+\frac{\partial^2\Phi_i(\eta,\eta_1,\eta_2,\eta_3)}{\partial x_3\partial x_2}\frac{\partial z_3^*}{\partial\bar{\tau}}+\frac{\partial^2\Phi_i(\eta,\eta_1,\eta_2,\eta_3)}{\partial\bar{\tau}\partial x_3}\left(\frac{-\acute{h}_0}{\acute{i}_0}+\frac{\partial z_3^*}{\partial\alpha}\right)\\&\left.+\frac{\partial^2\Phi_i(\eta,\eta_1,\eta_2,\eta_3)}{\partial x_1\partial x_3}\frac{\partial z_1^*}{\partial\bar{\tau}}\left(\frac{-\acute{h}_0}{\acute{i}_0}+\frac{\partial z_3^*}{\partial\alpha}\right)+\frac{\partial^2\Phi_i(\eta,\eta_1,\eta_2,\eta_3)}{\partial x_3^2}\frac{\partial z_3^*}{\partial\bar{\tau}}\left(\frac{-\acute{h}_0}{\acute{i}_0}+\frac{\partial z_3^*}{\partial\alpha}\right)\right\}.\end{aligned}$$

From (46), we have $\frac{\partial z_1^*(0,0)}{\partial\bar{\tau}}=\frac{1}{\acute{a}_0}\frac{\partial\Theta_1}{\partial x_1}\frac{\partial\Phi_1(\tau_0,X_0)}{\partial\bar{\tau}}$ and $\frac{\partial z_3^*(0,0)}{\partial\bar{\tau}}=0$.
From equations (39), (41) and (40), we obtain $\frac{\partial^2\Phi_2(t,X_0)}{\partial\bar{\tau}\partial x_1}=0$, $\frac{\partial^2\Phi_2(t,X_0)}{\partial\bar{\tau}\partial x_3}=0$ and $\frac{\partial^2\Phi_2(t,X_0)}{\partial\bar{\tau}\partial x_2}=\frac{\partial F_2(\zeta(t))}{\partial x_2}\exp\left(\int_0^t\frac{\partial F_2(\zeta(r))}{\partial x_2}dr\right)$, then

$$\begin{aligned}B_2=&-\frac{\partial^2\Theta_2(\Phi(\tau_0,X_0))}{\partial x_1\partial x_2}\frac{\partial\Phi_2(\tau_0,X_0)}{\partial x_2}\left(\frac{\partial\Phi_1(\tau_0,X_0)}{\partial\bar{\tau}}+\frac{\partial\Phi_1(\tau_0,X_0)}{\partial x_1}\frac{1}{\acute{a}_0}\frac{\partial\Theta_1}{\partial x_1}\frac{\partial\Phi_1(\tau_0,X_0)}{\partial\bar{\tau}}\right)\\&-\frac{\partial\Theta_2(\Phi(\tau_0,X_0))}{\partial x_2}\left\{\frac{\partial^2\Phi_2(\tau_0,X_0)}{\partial\bar{\tau}\partial x_2}+\frac{\partial^2\Phi_2(\tau_0,X_0)}{\partial x_1\partial x_2}\frac{1}{\acute{a}_0}\frac{\partial\Theta_1}{\partial x_1}\frac{\partial\Phi_1(\tau_0,X_0)}{\partial\bar{\tau}}\right\}.\end{aligned}$$

(C2) $\acute{e}_0\neq0$ and $\acute{i}_0=0$.
Calculation of A_3.
We have $\frac{\partial^2f_3}{\partial\bar{\tau}^2}=\frac{\partial^2}{\partial\bar{\tau}^2}(\eta_3-\Theta_3\circ\Phi(\eta,\eta_1,\eta_2,\eta_3))$, then

$$\begin{aligned}\frac{\partial^2f_3}{\partial\bar{\tau}^2}=&-\sum_{j=1}^3\sum_{i=1}^3\frac{\partial^2\Theta_3}{\partial x_i\partial x_j}\left(\frac{\partial\Phi_i(\eta,\eta_1,\eta_2,\eta_3)}{\partial\bar{\tau}}+\frac{\partial\Phi_i(\eta,\eta_1,\eta_2,\eta_3)}{\partial x_1}\frac{\partial z_1^*}{\partial\bar{\tau}}+\frac{\partial\Phi_i(\eta,\eta_1,\eta_2,\eta_3)}{\partial x_2}\frac{\partial z_2^*}{\partial\bar{\tau}}\right)\\&\times\left(\frac{\partial\Phi_j(\eta,\eta_1,\eta_2,\eta_3)}{\partial\bar{\tau}}+\frac{\partial\Phi_j(\eta,\eta_1,\eta_2,\eta_3)}{\partial x_1}\frac{\partial z_1^*}{\partial\bar{\tau}}+\frac{\partial\Phi_j(\eta,\eta_1,\eta_2,\eta_3)}{\partial x_2}\frac{\partial z_2^*}{\partial\bar{\tau}}\right)\\&-\sum_{i=1}^3\frac{\partial\Theta_3}{\partial x_i}\left\{\frac{\partial^2\Phi_i(\eta,\eta_1,\eta_2,\eta_3)}{\partial\bar{\tau}^2}+2\frac{\partial^2\Phi_i(\eta,\eta_1,\eta_2,\eta_3)}{\partial\bar{\tau}\partial x_1}\frac{\partial z_1^*}{\partial\bar{\tau}}+2\frac{\partial^2\Phi_i(\eta,\eta_1,\eta_2,\eta_3)}{\partial\bar{\tau}\partial x_2}\frac{\partial z_2^*}{\partial\bar{\tau}}\right.\\&+\frac{\partial^2\Phi_i(\eta,\eta_1,\eta_2,\eta_3)}{\partial x_1^2}\left(\frac{\partial z_1^*}{\partial\bar{\tau}}\right)^2+2\frac{\partial^2\Phi_i(\eta,\eta_1,\eta_2,\eta_3)}{\partial x_1\partial x_2}\frac{\partial z_1^*}{\partial\bar{\tau}}\frac{\partial z_2^*}{\partial\bar{\tau}}+\frac{\partial\Phi_i(\eta,\eta_1,\eta_2,\eta_3)}{\partial x_1}\frac{\partial^2z_1^*}{\partial\bar{\tau}^2}\\&\left.+\frac{\partial^2\Phi_i(\eta,\eta_1,\eta_2,\eta_3)}{\partial x_2^2}\left(\frac{\partial z_2^*}{\partial\bar{\tau}}\right)^2+\frac{\partial\Phi_i(\eta,\eta_1,\eta_2,\eta_3)}{\partial x_2}\frac{\partial^2z_2^*}{\partial\bar{\tau}^2}\right\}.\end{aligned}$$

We have $\frac{\partial^2\Theta_3(\Phi(\tau_0,X_0))}{\partial x_1^2} = \frac{\partial\Theta_3(\Phi(\tau_0,X_0))}{\partial x_1} = 0$, $\frac{\partial^2\Phi_2(\tau_0,X_0)}{\partial\bar{\tau}^2} = \frac{\partial^2\Phi_3(\tau_0,X_0)}{\partial\bar{\tau}^2} = 0$, $\frac{\partial\Phi_2(\tau_0,X_0)}{\partial x_1} = \frac{\partial\Phi_3(\tau_0,X_0)}{\partial x_1} = 0$ and $\frac{\partial\Phi_2(\tau_0,X_0)}{\partial\bar{\tau}} = \frac{\partial\Phi_3(\tau_0,X_0)}{\partial\bar{\tau}} = 0$.
From (39), (42) and (48), we have $\frac{\partial^2\Phi_2(\tau_0,X_0)}{\partial\tau\partial x_1} = \frac{\partial^2\Phi_2(\tau_0,X_0)}{\partial x_1^2} = 0$, $\frac{\partial^2\Phi_3(\tau_0,X_0)}{\partial\tau\partial x_1} = \frac{\partial^2\Phi_3(\tau_0,X_0)}{\partial x_1^2} = 0$, and $\frac{\partial z_2^*(0,0)}{\partial\bar{\tau}} = 0$ respectively.
From second partial derivative of equation (2.20), we have
$\frac{\partial^2 z_2^*(0,0)}{\partial\bar{\tau}^2}\left(1 - \frac{\partial\Theta_2(\Phi(\tau_0,X_0))}{\partial x_2}\frac{\partial\Phi_2(\tau_0,X_0)}{\partial x_2}\right) = \frac{\partial^2 z_2^*(0,0)}{\partial\bar{\tau}^2}\acute{e}_0 = 0$, then $\frac{\partial^2 z_2^*(0,0)}{\partial\bar{\tau}^2} = 0$.
Finally we obtain $A_3 = 0$.

Calculation of C_3.

We have $\frac{\partial^2 f_3}{\partial\alpha^2} = \frac{\partial^2}{\partial\alpha^2}(\eta_3 - \Theta_3\circ\Phi(\eta,\eta_1,\eta_2,\eta_3))$, then

$$\begin{aligned}
\frac{\partial^2 f_3}{\partial\alpha^2} &= -\sum_{j=1}^{3}\sum_{i=1}^{3}\frac{\partial^2\Theta_3}{\partial x_i\partial x_j}\\
&\times\left(\frac{\partial\Phi_i(\eta,\eta_1,\eta_2,\eta_3)}{\partial x_1}\left(\frac{-\acute{c}_0}{\acute{a}_0}+\frac{\partial z_1^*}{\partial\alpha}\right)+\frac{\partial\Phi_i(\eta,\eta_1,\eta_2,\eta_3)}{\partial x_2}\frac{\partial z_2^*}{\partial\alpha}+\frac{\partial\Phi_i(\eta,\eta_1,\eta_2,\eta_3)}{\partial x_3}\right)\\
&\times\left(\frac{\partial\Phi_j(\eta,\eta_1,\eta_2,\eta_3)}{\partial x_1}\left(\frac{-\acute{c}_0}{\acute{a}_0}+\frac{\partial z_1^*}{\partial\alpha}\right)+\frac{\partial\Phi_j(\eta,\eta_1,\eta_2,\eta_3)}{\partial x_2}\frac{\partial z_2^*}{\partial\alpha}+\frac{\partial\Phi_j(\eta,\eta_1,\eta_2,\eta_3)}{\partial x_3}\right)\\
&-\sum_{i=1}^{3}\frac{\partial\Theta_3}{\partial x_i}\Bigg\{\frac{\partial^2\Phi_i(\eta,\eta_1,\eta_2,\eta_3)}{\partial x_1^2}\left(\frac{-\acute{c}_0}{\acute{a}_0}+\frac{\partial z_1^*}{\partial\alpha}\right)^2+2\frac{\partial^2\Phi_i(\eta,\eta_1,\eta_2,\eta_3)}{\partial x_2\partial x_1}\frac{\partial z_2^*}{\partial\alpha}\left(\frac{-\acute{c}_0}{\acute{a}_0}+\frac{\partial z_1^*}{\partial\alpha}\right)\\
&+2\frac{\partial^2\Phi_i(\eta,\eta_1,\eta_2,\eta_3)}{\partial x_3\partial x_1}\left(\frac{-\acute{c}_0}{\acute{a}_0}+\frac{\partial z_1^*}{\partial\alpha}\right)+\frac{\partial\Phi_i(\eta,\eta_1,\eta_2,\eta_3)}{\partial x_1}\left(\frac{\partial^2 z_1^*}{\partial\alpha^2}\right)+\frac{\partial^2\Phi_i(\eta,\eta_1,\eta_2,\eta_3)}{\partial x_2^2}\left(\frac{\partial z_2^*}{\partial\alpha}\right)^2\\
&+2\frac{\partial^2\Phi_i(\eta,\eta_1,\eta_2,\eta_3)}{\partial x_3\partial x_2}\frac{\partial z_2^*}{\partial\alpha}+\frac{\partial\Phi_i(\eta,\eta_1,\eta_2,\eta_3)}{\partial x_2}\left(\frac{\partial^2 z_2^*}{\partial\alpha^2}\right)+\frac{\partial^2\Phi_i(\eta,\eta_1,\eta_2,\eta_3)}{\partial x_3^2}\Bigg\}.
\end{aligned}$$

To determine C_3 we must calculate (E_4): $\frac{\partial^2 z_2^*(0,0)}{\partial\alpha^2}$, ($E_5$): $\frac{\partial^2\Phi_3(\tau_0,X_0)}{\partial x_3\partial x_1}$ and (E_6): $\frac{\partial^2\Phi_3(\tau_0,X_0)}{\partial x_3^2}$.
(E_4): From the second partial derivative of equation (2.20), we have

$$\left(1 - \frac{\partial\Theta_2(\tau_0,X_0))}{\partial x_2}\frac{\partial\Phi_2(\tau_0,X_0)}{\partial x_2}\right)\frac{\partial^2 z_2^*(0,0)}{\partial\alpha^2} = \acute{e}_0\frac{\partial^2 z_2^*(0,0)}{\partial\alpha^2} = 0,$$

then $\frac{\partial^2 z_2^*(0,0)}{\partial\alpha^2} = 0$.
(E_5): The term $\frac{\partial^2\Phi_3(t,X_0)}{\partial x_3\partial x_1}$ can be obtained from the following linear differential equation

$$\begin{aligned}
\frac{d}{dt}\left(\frac{\partial^2\Phi_3(t,X_0)}{\partial x_3\partial x_1}\right) &= \frac{\partial F_3(\zeta(t))}{\partial x_1}\frac{\partial^2\Phi_1(t,X_0)}{\partial x_3\partial x_1}+\frac{\partial F_3(\zeta(t))}{\partial x_2}\frac{\partial^2\Phi_2(t,X_0)}{\partial x_3\partial x_1}+\frac{\partial F_3(\zeta(t))}{\partial x_3}\frac{\partial^2\Phi_3(t,X_0)}{\partial x_3\partial x_1}\\
&+\left(\frac{\partial^2 F_3(\zeta(t))}{\partial x_1^2}\frac{\partial\Phi_1(t,X_0)}{\partial x_3}+\frac{\partial^2 F_3(\zeta(t))}{\partial x_2\partial x_1}\frac{\partial\Phi_2(t,X_0)}{\partial x_3}+\frac{\partial^2 F_3(\zeta(t))}{\partial x_3\partial x_1}\frac{\partial\Phi_3(t,X_0)}{\partial x_3}\right)\frac{\partial\Phi_1(t,X_0)}{\partial x_1}\\
&+\left(\frac{\partial^2 F_3(\zeta(t))}{\partial x_1\partial x_2}\frac{\partial\Phi_1(t,X_0)}{\partial x_3}+\frac{\partial^2 F_3(\zeta(t))}{\partial x_2^2}\frac{\partial\Phi_2(t,X_0)}{\partial x_3}+\frac{\partial^2 F_3(\zeta(t))}{\partial x_3\partial x_2}\frac{\partial\Phi_3(t,X_0)}{\partial x_3}\right)\frac{\partial\Phi_2(t,X_0)}{\partial x_1}\\
&+\left(\frac{\partial^2 F_3(\zeta(t))}{\partial x_1\partial x_3}\frac{\partial\Phi_1(t,X_0)}{\partial x_3}+\frac{\partial^2 F_3(\zeta(t))}{\partial x_2\partial x_3}\frac{\partial\Phi_2(t,X_0)}{\partial x_3}+\frac{\partial^2 F_3(\zeta(t))}{\partial x_3^2}\frac{\partial\Phi_3(t,X_0)}{\partial x_3}\right)\frac{\partial\Phi_3(t,X_0)}{\partial x_1}
\end{aligned}$$

with the initial condition $\frac{\partial^2\Phi_3(0,X_0)}{\partial x_3\partial x_1} = 0$, then

$$\frac{d}{dt}\left(\frac{\partial^2\Phi_3(t,X_0)}{\partial x_3\partial x_1}\right) = \frac{\partial F_3(\zeta(t))}{\partial x_3}\frac{\partial^2\Phi_3(t,X_0)}{\partial x_3\partial x_1}+\frac{\partial^2 F_3(\zeta(t))}{\partial x_3\partial x_1}\frac{\partial\Phi_3(t,X_0)}{\partial x_3}\frac{\partial\Phi_1(t,X_0)}{\partial x_1}$$

with the initial condition $\frac{\partial^2\Phi_3(0,X_0)}{\partial x_3\partial x_1} = 0$. We obtain

$$\frac{\partial^2\Phi_3(t,X_0)}{\partial x_3\partial x_1} = \int_0^t\exp\left(\int_0^t\frac{\partial F_3(\zeta(s))}{\partial x_3}ds\right)\left(\frac{\partial^2 F_3(\zeta(r))}{\partial x_3\partial x_1}\right)\exp\left(\int_0^r\frac{\partial F_1(\zeta(s))}{\partial x_1}ds\right)dr.$$

(E_6): In the same way as above, we have

$$\begin{aligned}\frac{d}{dt}\left(\frac{\partial^2\Phi_3(t,X_0)}{\partial x_3^2}\right) = & \frac{\partial F_3(\zeta(t))}{\partial x_1}\frac{\partial^2\Phi_1(t,X_0)}{\partial x_3^2} + \frac{\partial F_3(\zeta(t))}{\partial x_2}\frac{\partial^2\Phi_2(t,X_0)}{\partial x_3^2} + \frac{\partial F_3(\zeta(t))}{\partial x_3}\frac{\partial^2\Phi_3(t,X_0)}{\partial x_3^2} \\ & + \left(\frac{\partial^2 F_3(\zeta(t))}{\partial x_1^2}\frac{\partial\Phi_1(t,X_0)}{\partial x_3} + \frac{\partial^2 F_3(\zeta(t))}{\partial x_2\partial x_1}\frac{\partial\Phi_2(t,X_0)}{\partial x_3} + \frac{\partial^2 F_3(\zeta(t))}{\partial x_3\partial x_1}\frac{\partial\Phi_3(t,X_0)}{\partial x_3}\right)\frac{\partial\Phi_1(t,X_0)}{\partial x_3} \\ & + \left(\frac{\partial^2 F_3(\zeta(t))}{\partial x_1\partial x_2}\frac{\partial\Phi_1(t,X_0)}{\partial x_3} + \frac{\partial^2 F_3(\zeta(t))}{\partial x_2^2}\frac{\partial\Phi_2(t,X_0)}{\partial x_3} + \frac{\partial^2 F_3(\zeta(t))}{\partial x_3\partial x_2}\frac{\partial\Phi_3(t,X_0)}{\partial x_3}\right)\frac{\partial\Phi_2(t,X_0)}{\partial x_3} \\ & + \left(\frac{\partial^2 F_3(\zeta(t))}{\partial x_1\partial x_3}\frac{\partial\Phi_1(t,X_0)}{\partial x_3} + \frac{\partial^2 F_3(\zeta(t))}{\partial x_2\partial x_3}\frac{\partial\Phi_2(t,X_0)}{\partial x_3} + \frac{\partial^2 F_3(\zeta(t))}{\partial x_3^2}\frac{\partial\Phi_3(t,X_0)}{\partial x_3}\right)\frac{\partial\Phi_3(t,X_0)}{\partial x_3}\end{aligned}$$

with the initial condition $\frac{\partial^2\Phi_3(0,X_0)}{\partial x_3^2} = 0$, then

$$\begin{aligned}\frac{d}{dt}\left(\frac{\partial^2\Phi_3(t,X_0)}{\partial x_3^2}\right) &= \frac{\partial F_3(\zeta(t))}{\partial x_3}\frac{\partial^2\Phi_3(t,X_0)}{\partial x_3^2} \\ &+ \left(2\frac{\partial^2 F_3(\zeta(t))}{\partial x_3\partial x_1}\frac{\partial\Phi_1(t,X_0)}{\partial x_3} + \frac{\partial^2 F_3(\zeta(t))}{\partial x_3^2}\frac{\partial\Phi_3(t,X_0)}{\partial x_3}\right)\frac{\partial\Phi_3(t,X_0)}{\partial x_3}\end{aligned}$$

with the initial condition $\frac{\partial^2\Phi_3(0,X_0)}{\partial x_3^2} = 0$. We obtain

$$\frac{\partial^2\Phi_3(t,X_0)}{\partial x_3^2} = \exp\left(\int_0^t \frac{\partial F_3(\zeta(s))}{\partial x_3}ds\right)\int_0^t\left(2\frac{\partial^2 F_3(\zeta(r))}{\partial x_3\partial x_1}\frac{\partial\Phi_1(r,X_0)}{\partial x_3} + \frac{\partial^2 F_3(\zeta(r))}{\partial x_3^2}\frac{\partial\Phi_3(r,X_0)}{\partial x_3}\right)dr.$$

Therefore

$$\begin{aligned}C_3 = & -2\frac{\partial^2\Theta_3(\Phi(\tau_0,X_0))}{\partial x_1\partial x_3}\left(\frac{\partial\Phi_1(\tau_0,X_0)}{\partial x_1}\left(\frac{-\acute{c}_0}{\acute{a}_0}\right) + \frac{\partial\Phi_1(\tau_0,X_0)}{\partial x_3}\right)\frac{\partial\Phi_3(\tau_0,X_0)}{\partial x_3} \\ & -\frac{\partial\Theta_3(\Phi(\tau_0,X_0))}{\partial x_3}\left\{2\frac{\partial^2\Phi_3(\tau_0,X_0)}{\partial x_3\partial x_1}\left(\frac{-\acute{c}_0}{\acute{a}_0}\right) + \frac{\partial^2\Phi_3(\tau_0,X_0)}{\partial x_3^2}\right\} - \frac{\partial^2\Theta_3(\Phi(\tau_0,X_0))}{\partial x_3^2}\left(\frac{\partial\Phi_3(\tau_0,X_0)}{\partial x_3}\right)^2.\end{aligned}$$

Calculation of B_3.

We have $\frac{\partial^2 f_3}{\partial\bar{\tau}\partial\alpha} = \frac{\partial}{\partial\bar{\tau}}\left(\frac{\partial}{\partial\alpha}(\eta_3 - \Theta_3\circ\Phi(\eta,\eta_1,\eta_2,\eta_3))\right)$, then

$$\begin{aligned}\frac{\partial^2 f_3}{\partial\bar{\tau}\partial\alpha} = & -\sum_{j=1}^{3}\sum_{i=1}^{3}\frac{\partial^2\Theta_3}{\partial x_i\partial x_j}\left(\frac{\partial\Phi_i(\eta,\eta_1,\eta_2,\eta_3)}{\partial\bar{\tau}} + \frac{\partial\Phi_i(\eta,\eta_1,\eta_2,\eta_3)}{\partial x_1}\frac{\partial z_1^*}{\partial\bar{\tau}} + \frac{\partial\Phi_i(\eta,\eta_1,\eta_2,\eta_3)}{\partial x_2}\frac{\partial z_2^*}{\partial\bar{\tau}}\right) \\ & \times\left(\frac{\partial\Phi_j(\eta,\eta_1,\eta_2,\eta_3)}{\partial x_1}\left(\frac{-\acute{c}_0}{\acute{a}_0} + \frac{\partial z_1^*}{\partial\alpha}\right) + \frac{\partial\Phi_j(\eta,\eta_1,\eta_2,\eta_3)}{\partial x_2}\frac{\partial z_2^*}{\partial\alpha} + \frac{\partial\Phi_j(\eta,\eta_1,\eta_2,\eta_3)}{\partial x_3}\right) \\ & -\sum_{i=1}^{3}\frac{\partial\Theta_3}{\partial x_i}\left\{\left(\frac{\partial^2\Phi_i(\eta,\eta_1,\eta_2,\eta_3)}{\partial\bar{\tau}\partial x_1} + \frac{\partial^2\Phi_i(\eta,\eta_1,\eta_2,\eta_3)}{\partial x_1^2}\frac{\partial z_1^*}{\partial\bar{\tau}} + \frac{\partial^2\Phi_i(\eta,\eta_1,\eta_2,\eta_3)}{\partial x_2\partial x_1}\frac{\partial z_2^*}{\partial\bar{\tau}}\right)\left(\frac{-\acute{c}_0}{\acute{a}_0} + \frac{\partial z_1^*}{\partial\alpha}\right)\right. \\ & + \frac{\partial\Phi_i(\eta,\eta_1,\eta_2,\eta_3)}{\partial x_1}\frac{\partial^2 z_1^*}{\partial\bar{\tau}\partial\alpha} + \left(\frac{\partial^2\Phi_i(\eta,\eta_1,\eta_2,\eta_3)}{\partial\bar{\tau}\partial x_2} + \frac{\partial^2\Phi_i(\eta,\eta_1,\eta_2,\eta_3)}{\partial x_1\partial x_2}\frac{\partial z_1^*}{\partial\bar{\tau}} + \frac{\partial^2\Phi_i(\eta,\eta_1,\eta_2,\eta_3)}{\partial x_2^2}\frac{\partial z_2^*}{\partial\bar{\tau}}\right)\frac{\partial z_2^*}{\partial\alpha} \\ & \left. + \frac{\partial\Phi_i(\eta,\eta_1,\eta_2,\eta_3)}{\partial x_2}\frac{\partial^2 z_2^*}{\partial\bar{\tau}\partial\alpha} + \frac{\partial^2\Phi_i(\eta,\eta_1,\eta_2,\eta_3)}{\partial\bar{\tau}\partial x_3} + \frac{\partial^2\Phi_i(\eta,\eta_1,\eta_2,\eta_3)}{\partial x_1\partial x_3}\frac{\partial z_1^*}{\partial\bar{\tau}} + \frac{\partial^2\Phi_i(\eta,\eta_1,\eta_2,\eta_3)}{\partial x_2\partial x_3}\frac{\partial z_2^*}{\partial\bar{\tau}}\right\}.\end{aligned}$$

From (48), we have $\frac{\partial z_1^*(0,0)}{\partial\bar{\tau}} = \frac{1}{\acute{a}_0}\frac{\partial\Theta_1(\Phi(\tau_0,X_0))}{\partial x_1}\frac{\partial\Phi_1(\tau_0,X_0)}{\partial\bar{\tau}}$ and $\frac{\partial z_2^*(0,0)}{\partial\bar{\tau}} = 0$.
From the second partial derivative of equation (2.20), we have

$$\left(1 - \frac{\partial\Theta_2(\Phi(\tau_0,X_0))}{\partial x_2}\frac{\partial\Phi_2(\tau_0,X_0)}{\partial x_2}\right)\frac{\partial^2 z_2^*(0,0)}{\partial\bar{\tau}\partial\alpha} = \acute{e}_0\frac{\partial^2 z_2^*(0,0)}{\partial\bar{\tau}\partial\alpha} = 0$$

From equations (39), (41), (42) and (44), we have $\frac{\partial^2\Phi_2(t,X_0)}{\partial\bar{\tau}\partial x_1} = 0$, $\frac{\partial^2\Phi_2(t,X_0)}{\partial\bar{\tau}\partial x_3} = 0$, $\frac{\partial^2\Phi_3(t,X_0)}{\partial\bar{\tau}\partial x_1} = 0$ and $\frac{\partial^2\Phi_3(t,X_0)}{\partial\bar{\tau}\partial x_3} = \frac{\partial F_3(\zeta(t))}{\partial x_3}\exp\left(\int_0^t\frac{\partial F_3(\zeta(r))}{\partial x_3}dr\right)$. We obtain

$$\begin{aligned}B_3 = & -\frac{\partial\Theta_3(\Phi(\tau_0,X_0))}{\partial x_3}\left\{\frac{\partial^2\Phi_3(\tau_0,X_0)}{\partial\bar{\tau}\partial x_3} + \frac{\partial^2\Phi_3(\tau_0,X_0)}{\partial x_1\partial x_3}\frac{\partial z_1^*(0,0)}{\partial\bar{\tau}}\right\} \\ & -\frac{\partial^2\Theta_3(\Phi(\tau_0,X_0))}{\partial x_1\partial x_3}\left\{\frac{\partial\Phi_1(\tau_0,X_0)}{\partial\bar{\tau}} + \frac{\partial\Phi_1(\tau_0,X_0)}{\partial x_1}\frac{\partial z_1^*(0,0)}{\partial\bar{\tau}}\right\}\frac{\partial\Phi_3(\tau_0,X_0)}{\partial x_3}.\end{aligned}$$

4.5. **The cancer model cases.** In the following, we calculate all parameters and partial differential equation terms in different cases.
$\frac{\partial\Theta_i}{\partial x_i} = T_i$, $(i \neq 2)$, $\frac{\partial\Theta_2}{\partial x_2} = T_2 - R$,
$\frac{\partial\Theta_i}{\partial x_j} = 0$, $(i \neq j$ and $(i,j) \neq (3,2))$, $\frac{\partial\Theta_3}{\partial x_2} = R$,
$\frac{\partial\Phi_1(\tau_0,X_0)}{\partial x_1} = T_1^{-2}e^{-r_1\tau_0}$,
$\frac{\partial\Phi_2(\tau_0,X_0)}{\partial x_2} = T_1^{\frac{-r_2\lambda_2 K_1}{r_1}} e^{(r_2-r_2\lambda_2K_1-m)\tau_0}$,
$\frac{\partial\Phi_3(\tau_0,X_0)}{\partial x_3} = T_1^{\frac{-r_3\lambda_3 K_1}{r_1}} e^{(r_3-r_3\lambda_3K_1)\tau_0}$,
$\frac{\partial\Phi_3(\tau_0,X_0)}{\partial x_2} = \frac{me^{(1-\lambda_3K_1)r_3\tau_0}(1-e^{-r_1\tau_0})^{\frac{r_2\lambda_2K_1}{r_1}}}{T_1^{\frac{r_3\lambda_3K_1}{r_1}}(1-e^{-r_1\tau_0})^{\frac{r_3\lambda_3K_1}{r_1}}}\int_0^{\tau_0}\frac{e^{(r_2-r_3-m)u}}{((T_1-e^{-r_1\tau_0})e^{r_1u}+(1-T_1))^{\frac{K_1(r_2\lambda_2-r_3\lambda_3)}{r_1}}}du$,
$\frac{\partial\Phi_1(\tau_0,X_0)}{\partial x_3} = -\frac{r_1\lambda_1K_1(T_1-e^{-r_1\tau_0})e^{-r_1\tau_0}}{T_1^2(1-e^{-r_1\tau_0})^{2-\frac{r_3\lambda_3K_1}{r_1}}}\int_0^{\tau_0}e^{r_3u}((T_1-e^{-r_1\tau_0})e^{r_1u}+(1-T_1))^{1-\frac{r_3\lambda_3K_1}{r_1}}du$,

$$\begin{aligned}\frac{\partial\Phi_1(\tau_0,X_0)}{\partial x_2} &= -\frac{r_1\lambda_1K_1(T_1-e^{-r_1\tau_0})e^{-r_1\tau_0}}{T_1^2(1-e^{-r_1\tau_0})^{2-\frac{r_2\lambda_2K_1}{r_1}}}\Bigg\{\int_0^{\tau_0}\frac{e^{(r_2-m)u}}{((T_1-e^{-r_1\tau_0})e^{r_1u}+(1-T_1))^{\frac{r_2\lambda_2K_1}{r_1}-1}}du \\ &+ m\int_0^{\tau_0}\frac{\int_0^u e^{(r_2-r_3-m)p}((T_1-e^{-r_1\tau_0})e^{r_1p}+(1-T_1))^{(r_3\lambda_3-r_2\lambda_2)\frac{K_1}{r_1}}dp}{e^{-r_3u}((T_1-e^{-r_1\tau_0})e^{r_1u}+(1-T_1))^{\frac{r_3\lambda_3K_1}{r_1}-1}}du\Bigg\},\end{aligned}$$

$\acute{a_0} = T_1^{-1}(T_1 - e^{-r_1\tau_0})$,

$$\begin{aligned}\acute{b_0} &= \frac{r_1\lambda_1K_1(T_1-e^{-r_1\tau_0})e^{-r_1\tau_0}}{T_1(1-e^{-r_1\tau_0})^{2-\frac{r_2\lambda_2K_1}{r_1}}}\Bigg\{\int_0^{\tau_0}\frac{e^{(r_2-m)u}}{((T_1-e^{-r_1\tau_0})e^{r_1u}+(1-T_1))^{\frac{r_2\lambda_2K_1}{r_1}-1}}du \\ &+ m\int_0^{\tau_0}\frac{\int_0^u e^{(r_2-r_3-m)p}((T_1-e^{-r_1\tau_0})e^{r_1p}+(1-T_1))^{(r_3\lambda_3-r_2\lambda_2)\frac{K_1}{r_1}}dp}{e^{-r_3u}((T_1-e^{-r_1\tau_0})e^{r_1u}+(1-T_1))^{\frac{r_3\lambda_3K_1}{r_1}-1}}du\Bigg\},\end{aligned}$$

$\acute{c_0} = \frac{r_1\lambda_1K_1(T_1-e^{-r_1\tau_0})e^{-r_1\tau_0}}{T_1(1-e^{-r_1\tau_0})^{2-\frac{r_3\lambda_3K_1}{r_1}}}\int_0^{\tau_0}e^{r_3u}((T_1-e^{-r_1\tau_0})e^{r_1u}+(1-T_1))^{1-\frac{r_3\lambda_3K_1}{r_1}}du$,

$\acute{d_0} = 0$, $\acute{e_0} = 1-(T_2-R)T_1^{\frac{-r_2\lambda_2K_1}{r_1}}e^{(r_2-r_2\lambda_2K_1-m)\tau_0}$, $\acute{f_0} = 0$, $\acute{g_0} = 0$,

$$\begin{aligned}\acute{h_0} &= -RT_1^{\frac{-r_2\lambda_2K_1}{r_1}}e^{(r_2-r_2\lambda_2K_1-m)\tau_0} \\ &- \frac{mT_3e^{(1-\lambda_3K_1)r_3\tau_0}(1-e^{-r_1\tau_0})^{\frac{r_2\lambda_2K_1}{r_1}}}{T_1^{\frac{r_3\lambda_3K_1}{r_1}}(1-e^{-r_1\tau_0})^{\frac{r_3\lambda_3K_1}{r_1}}}\int_0^{\tau_0}\frac{e^{(r_2-r_3-m)u}}{((T_1-e^{-r_1\tau_0})e^{r_1u}+(1-T_1))^{\frac{K_1(r_2\lambda_2-r_3\lambda_3)}{r_1}}}du\end{aligned}$$

and $\acute{i_0} = 1 - T_3T_1^{\frac{-r_3\lambda_3K_1}{r_1}}e^{(r_3-r_3\lambda_3K_1)\tau_0}$.
(C1) $\acute{e_0} = 0$ and $\acute{i_0} \neq 0$.
We have
$\frac{\partial^2\Phi_2(\tau_0,X_0)}{\partial x_2\partial x_1} = \frac{r_2\lambda_2e^{(r_2-r_2\lambda_2K_1-m)\tau_0}}{r_1T_1^{\frac{r_1+r_2\lambda_2K_1}{r_1}}}(e^{-r_1\tau_0}-1)$,

$$\begin{aligned}\frac{\partial^2\Phi_2(\tau_0,X_0)}{\partial x_3\partial x_2} &= r_1r_2\lambda_1\lambda_2k_1e^{(r_2(1-\lambda_2k_1)-m)\tau_0}\frac{T_1^{\frac{-r_2\lambda_2K_1}{r_1}}(T_1-e^{-r_1\tau_0})}{(1-e^{-r_1\tau_0})^{-\frac{r_3\lambda_3K_1}{r_1}}} \\ &\times\int_0^{\tau_0}\frac{e^{r_1u}}{((T_1-e^{-r_1\tau_0})e^{r_1u}+(1-T_1))^2}\left(\int_0^u\frac{e^{r_3s}}{((T_1-e^{-r_1\tau_0})e^{r_1s}+(1-T_1))^{\frac{r_3\lambda_3k_1}{r_1}-1}}ds\right)du \\ &-e^{(r_2(1-\lambda_2k_1)-m)\tau_0}\frac{r_2(1+\lambda_2k_2)T_1^{\frac{-r_2\lambda_2K_1}{r_1}}}{k_2(1-e^{-r_1\tau_0})^{\frac{-r_3\lambda_3K_1}{r_1}}}\int_0^{\tau_0}e^{r_3u}((T_1-e^{-r_1\tau_0})e^{r_1u}+(1-T_1))^{\frac{-r_3\lambda_3K_1}{r_1}}du,\end{aligned}$$

$$\frac{\partial^2\Phi_2(\tau_0,X_0)}{\partial x_2^2} = \frac{2r_1r_2\lambda_1\lambda_2k_1e^{(r_2(1-\lambda_2k_1)-m)\tau_0}(T_1-e^{-r_1\tau_0})}{T_1^{\frac{r_2\lambda_2K_1}{r_1}}(1-e^{-r_1\tau_0})^{\frac{-r_2\lambda_2K_1}{r_1}}}\int_0^{\tau_0}e^{r_1u}\int_0^u\frac{((T_1-e^{-r_1\tau_0})e^{r_1u}+(1-T_1))^{-2}}{((T_1-e^{-r_1\tau_0})e^{r_1s}+(1-T_1))^{-1}}$$
$$\times\left(\frac{((T_1-e^{-r_1\tau_0})e^{r_1s}+(1-T_1))^{\frac{-r_2\lambda_2K_1}{r_1}}}{e^{-(r_2-m)s}(1-e^{-r_1\tau_0})^{\frac{r_2\lambda_2K_1}{r_1}}}+m\int_0^s\frac{((T_1-e^{-r_1\tau_0})e^{r_1s}+(1-T_1))^{\frac{-r_3\lambda_3K_1}{r_1}}e^{(r_3+r_2-m)r}}{e^{r_3s}((T_1-e^{-r_1\tau_0})e^{r_1r}+(1-T_1))^{\frac{(r_2\lambda_2-r_3\lambda_3)K_1}{r_1}}}dr\right)dsdu$$
$$-\frac{r_2e^{(r_2(1-\lambda_2k_1)-m)\tau_0}T_1^{\frac{-r_2\lambda_2K_1}{r_1}}}{k_2(1-e^{-r_1\tau_0})^{\frac{-r_2\lambda_2K_1}{r_1}}}\int_0^{\tau_0}e^{(r_2-m)u}((T_1-e^{-r_1\tau_0})e^{r_1u}+(1-T_1))^{\frac{-r_2\lambda_2K_1}{r_1}}du$$
$$-\frac{2r_2me^{(r_2-m)\tau_0}(T_1e^{r_1\tau_0})^{\frac{-r_2\lambda_2K_1}{r_1}}}{k_2(1-e^{-r_1\tau_0})^{\frac{-r_2\lambda_2K_1}{r_1}}}\int_0^{\tau_0}e^{r_3u}\int_0^u\frac{((T_1-e^{-r_1\tau_0})e^{r_1u}+(1-T_1))^{\frac{-r_3\lambda_3K_1}{r_1}}}{((T_1-e^{-r_1\tau_0})e^{r_1s}+(1-T_1))^{\frac{(r_2\lambda_2-r_3\lambda_3)K_1}{r_1}}}e^{(r_2-r_3-m)s}dsdu.$$

We obtain

$$C_2 = -2(T_2-R)\left(\frac{c_0'h_0'-b_0'i_0'}{a_0'i_0'}\right)\frac{r_2\lambda_2e^{(r_2-r_2\lambda_2K_1-m)\tau_0}}{r_1T_1^{\frac{r_1+r_2\lambda_2K_1}{r_1}}}(e^{-r_1\tau_0}-1)$$
$$-(T_2-R)\left\{\frac{2r_1r_2\lambda_1\lambda_2k_1e^{(r_2(1-\lambda_2k_1)-m)\tau_0}(T_1-e^{-r_1\tau_0})}{T_1^{\frac{r_2\lambda_2K_1}{r_1}}(1-e^{-r_1\tau_0})^{\frac{-r_2\lambda_2K_1}{r_1}}}\int_0^{\tau_0}e^{r_1u}\int_0^u\frac{((T_1-e^{-r_1\tau_0})e^{r_1u}+(1-T_1))^{-2}}{((T_1-e^{-r_1\tau_0})e^{r_1s}+(1-T_1))^{-1}}\right.$$
$$\times\left(\frac{((T_1-e^{-r_1\tau_0})e^{r_1s}+(1-T_1))^{\frac{-r_2\lambda_2K_1}{r_1}}}{e^{-(r_2-m)s}(1-e^{-r_1\tau_0})^{\frac{r_2\lambda_2K_1}{r_1}}}+m\int_0^s\frac{((T_1-e^{-r_1\tau_0})e^{r_1s}+(1-T_1))^{\frac{-r_3\lambda_3K_1}{r_1}}e^{(r_3+r_2-m)r}}{e^{r_3s}((T_1-e^{-r_1\tau_0})e^{r_1r}+(1-T_1))^{\frac{(r_2\lambda_2-r_3\lambda_3)K_1}{r_1}}}dr\right)dsdu$$
$$-\frac{r_2e^{(r_2(1-\lambda_2k_1)-m)\tau_0}T_1^{\frac{-r_2\lambda_2K_1}{r_1}}}{k_2(1-e^{-r_1\tau_0})^{\frac{-r_2\lambda_2K_1}{r_1}}}\int_0^{\tau_0}e^{(r_2-m)u}((T_1-e^{-r_1\tau_0})e^{r_1u}+(1-T_1))^{\frac{-r_2\lambda_2K_1}{r_1}}du$$
$$\left.-\frac{2r_2me^{(r_2-m)\tau_0}(T_1e^{r_1\tau_0})^{\frac{-r_2\lambda_2K_1}{r_1}}e^{(r_2-r_3-m)s}}{k_2(1-e^{-r_1\tau_0})^{\frac{-r_2\lambda_2K_1}{r_1}}}\int_0^{\tau_0}e^{r_3u}\int_0^u\frac{((T_1-e^{-r_1\tau_0})e^{r_1u}+(1-T_1))^{\frac{-r_3\lambda_3K_1}{r_1}}}{((T_1-e^{-r_1\tau_0})e^{r_1s}+(1-T_1))^{\frac{(r_2\lambda_2-r_3\lambda_3)K_1}{r_1}}}dsdu\right\}$$
$$-2(T_2-R)\left(\frac{-h_0'}{i_0'}\right)\left\{r_1r_2\lambda_1\lambda_2k_1e^{(r_2(1-\lambda_2k_1)-m)\tau_0}\frac{T_1^{\frac{-r_2\lambda_2K_1}{r_1}}(T_1-e^{-r_1\tau_0})}{(1-e^{-r_1\tau_0})^{-\frac{r_3\lambda_3K_1}{r_1}}}\right.$$
$$\times\int_0^{\tau_0}\frac{e^{r_1u}}{((T_1-e^{-r_1\tau_0})e^{r_1u}+(1-T_1))^2}\left(\int_0^u\frac{e^{r_3s}}{((T_1-e^{-r_1\tau_0})e^{r_1s}+(1-T_1))^{\frac{r_3\lambda_3k_1}{r_1}-1}}ds\right)du$$
$$\left.-e^{(r_2(1-\lambda_2k_1)-m)\tau_0}\frac{r_2(1+\lambda_2k_2)T_1^{\frac{-r_2\lambda_2K_1}{r_1}}}{k_2(1-e^{-r_1\tau_0})^{\frac{-r_3\lambda_3K_1}{r_1}}}\int_0^{\tau_0}e^{r_3u}((T_1-e^{-r_1\tau_0})e^{r_1u}+(1-T_1))^{\frac{-r_3\lambda_3K_1}{r_1}}du\right\}.$$

$$\frac{\partial\Phi_1(\tau_0,X_0)}{\partial\bar{\tau}} = \dot{x}_s(\tau_0) = \frac{r_1K_1(1-T_1)(T_1-e^{-r_1\tau_0})e^{-r_1\tau_0}}{T_1^2(1-e^{-r_1\tau_0})^2},$$
$$\frac{\partial z_1^*(0,0)}{\partial\bar{\tau}} = \frac{r_1K_1(1-T_1)e^{-r_1\tau_0}}{(1-e^{-r_1\tau_0})^2},$$
$$\frac{\partial^2\Phi_2(\tau_0,X_0)}{\partial\bar{\tau}\partial x_2} = \left(r_2-m-\frac{r_2\lambda_2K_1(T_1-e^{-r_1\tau_0})}{T_1(1-e^{-r_1\tau_0})}\right)T_1^{\frac{-r_2\lambda_2K_1}{r_1}}e^{(r_2-r_2\lambda_2K_1-m)\tau_0}.$$

We obtain

$$\frac{\partial^2\Phi_2(\tau_0,X_0)}{\partial x_2\partial x_1} = \frac{r_2\lambda_2e^{(r_2-r_2\lambda_2K_1-m)\tau_0}}{r_1T_1^{\frac{r_1+r_2\lambda_2K_1}{r_1}}}(e^{-r_1\tau_0}-1),$$

$$B_2 = -(T_2-R)\left(r_2-m-\frac{r_2\lambda_2K_1(T_1-e^{-r_1\tau_0})}{T_1(1-e^{-r_1\tau_0})}\right)T_1^{\frac{-r_2\lambda_2K_1}{r_1}}e^{(r_2-r_2\lambda_2K_1-m)\tau_0}$$
$$+(T_2-R)\frac{r_2\lambda_2e^{(r_2-r_2\lambda_2K_1-m)\tau_0}}{T_1^{\frac{r_1+r_2\lambda_2K_1}{r_1}}}\frac{K_1(1-T_1)(T_1-e^{-r_1\tau_0})e^{-r_1\tau_0}}{(1-e^{-r_1\tau_0})^2}.$$

(C2) $e_0' \neq 0$ and $i_0' = 0$.

We have $\frac{\partial^2\Phi_3(\tau_0,X_0)}{\partial x_3\partial x_1} = -\frac{r_3\lambda_3}{r_1}T_1^{-1-\frac{r_3\lambda_3K_1}{r_1}}(1-e^{-r_1\tau_0})e^{r_3\tau_0(1-\lambda_3K_1)}$,

$$
\begin{aligned}
\frac{\partial^2\Phi_3(\tau_0,X_0)}{\partial x_3^2} = \quad & \frac{2\lambda_1\lambda_3 r_1 r_3 k_1 (T_1-e^{-r_1\tau_0})}{(1-e^{-r_1\tau_0})^{-\frac{r_3\lambda_3 K_1}{r_1}}} \int_0^{\tau_0} \frac{e^{r_1 p}\left(\int_0^p e^{r_3 u}[(T_1-e^{-r_1\tau_0})e^{r_1 u}+(1-T_1)]^{1-\frac{r_3\lambda_3 K_1}{r_1}} du\right)}{T_1^{\frac{r_3\lambda_3 K_1}{r_1}} e^{-r_3(1-\lambda_3 K_1)\tau_0}[(T_1-e^{-r_1\tau_0})e^{r_1 p}+(1-T_1)]^2} dp \\
& -\frac{2r_3}{k_3} e^{r_3(1-\lambda_3 K_1)\tau_0} T_1^{\frac{-r_3\lambda_3 K_1}{r_1}} \int_0^{\tau_0} e^{r_3 u}\left(\frac{(T_1-e^{-r_1\tau_0})e^{r_1 u}+(1-T_1)}{1-e^{-r_1\tau_0}}\right)^{-\frac{r_3\lambda_3 K_1}{r_1}} du.
\end{aligned}
$$

We obtain

$$
\begin{aligned}
C_3 = \quad & 2T_3 \frac{r_3\lambda_3}{r_1} T_1^{-1-\frac{r_3\lambda_3 K_1}{r_1}} (1-e^{-r_1\tau_0}) e^{r_3\tau_0(1-\lambda_3 K_1)} \left(\frac{-c_0'}{a_0'}\right) \\
& -T_3 \left\{ \frac{2\lambda_1\lambda_3 r_1 r_3 k_1 (T_1-e^{-r_1\tau_0})}{(1-e^{-r_1\tau_0})^{-\frac{r_3\lambda_3 K_1}{r_1}}} \int_0^{\tau_0} \frac{e^{r_1 p}\left(\int_0^p e^{r_3 u}[(T_1-e^{-r_1\tau_0})e^{r_1 u}+(1-T_1)]^{1-\frac{r_3\lambda_3 K_1}{r_1}} du\right)}{T_1^{\frac{r_3\lambda_3 K_1}{r_1}} e^{-r_3(1-\lambda_3 K_1)\tau_0}[(T_1-e^{-r_1\tau_0})e^{r_1 p}+(1-T_1)]^2} dp \right. \\
& \left. -\frac{2r_3}{k_3} e^{r_3(1-\lambda_3 K_1)\tau_0} T_1^{\frac{-r_3\lambda_3 K_1}{r_1}} \int_0^{\tau_0} e^{r_3 u}\left(\frac{(T_1-e^{-r_1\tau_0})e^{r_1 u}+(1-T_1)}{1-e^{-r_1\tau_0}}\right)^{-\frac{r_3\lambda_3 K_1}{r_1}} du \right\}.
\end{aligned}
$$

$\frac{\partial z_1^*(0,0)}{\partial \bar{\tau}} = \frac{r_1 K_1 (1-T_1) e^{-r_1\tau_0}}{(1-e^{-r_1\tau_0})^2}$,

$\frac{\partial^2\Phi_3(\tau_0,X_0)}{\partial\bar{\tau}\partial x_3} = r_3\left(1-\frac{\lambda_3 K_1 (T_1-e^{-r_1\tau_0})e^{r_1\tau_0}}{T_1(e^{r_1\tau_0}-1)}\right) T_1^{\frac{-r_3\lambda_3 K_1}{r_1}} e^{(r_3-r_3\lambda_3 K_1)\tau_0}$.

We obtain

$$
\begin{aligned}
B_3 \quad = \quad & -r_3\left(1-\frac{\lambda_3 K_1 (T_1-e^{-r_1\tau_0})e^{r_1\tau_0}}{T_1(e^{r_1\tau_0}-1)}\right) T_3 T_1^{\frac{-r_3\lambda_3 K_1}{r_1}} e^{(r_3-r_3\lambda_3 K_1)\tau_0} \\
+ \quad & T_3 T_1^{-1-\frac{r_3\lambda_3 K_1}{r_1}} (1-e^{-r_1\tau_0}) e^{r_3\tau_0(1-\lambda_3 K_1)} \frac{r_3\lambda_3 K_1 (1-T_1) e^{-r_1\tau_0}}{(1-e^{-r_1\tau_0})^2}.
\end{aligned}
$$

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