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Chronic myeloid leukemia model

with periodic pulsed treatment

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ABSTRACT. In this work we develop a mathematical model of chronic myeloid leukemia including treatment with instantaneous effects. Our analysis focuses on the values of growth rate γ which give either stability or instability of the disease free equilibrium. If the growth rate γ of sensitive leukemic stem cells is less than some threshold γ^*, we obtain the stability of disease free equilibrium which means that the disease is eradicated for any period of treatment τ_0. Otherwise, for γ great than γ^*, the period of treatment must be less than some specific value τ_0^*. In the critical case when the period of treatment is equal to τ_0^*, we observe a persistence of the tumor, which means that the disease is viable.

KEYWORDS : Positive solution, impulsive differential equation, Fixed point theorem, Bifurcation.

In this work we are interested by the study of a mathematical model of chronic myeloid leukemia. The chronic myeloid leukemia is a cancer of the bone marrow and blood which is characterized by an abnormal proliferation of blood cells, usually white blood cells. This disease is a myelo-proliferative disorder characterized by the expansion of a clone of hematopoietic cells that carries the Philadelphia chromosome (Ph). The Ph-chromosome results from a reciprocal translocation between the long arms of chromosomes 9 and 22.
In this paper, we study a mathematical model of chronic myeloid leukemia (CML) under treatment, the model studied here is inspired from [9] and [16].
Several recent works have been developed to study the dynamics of CML under chemotherapy treatment, see ([14], [15], [16] and [17]).
More specifically, we consider the following mathematical model which is an extension of the model proposed in [9]. In our model, we assume that normal (resp. leukemic) cells differentiate through two stages of their life cycle, beginning with normal (resp. sensitive leukemic) stem cells which produce normal (resp. leukemic) progenitor cells.
The mathematical form of the system we shall investigate is the following

$$\begin{cases} \dot{x}_0 = (\beta - a_x - \beta_0 x_0 - \lambda(x_1 + y_1))x_0, \\ \dot{x}_1 = a_x x_0 - d_1 x_1, \\ \dot{y}_0 = (\gamma - a_y - \gamma_0 y_0 - \lambda(x_1 + \alpha y_1))y_0, \\ \dot{y}_1 = a_y y_0 - d_2 y_1, \end{cases} \tag{1}$$

with initial conditions

$$x_0(0) \geq 0, x_1(0) \geq 0, y_0(0) \geq 0 \text{ and } y_1(0) \geq 0. \tag{2}$$

Throughout this paper, we assume the following conditions

$$a_y < \gamma, \tag{3}$$

and

$$a_x < \beta. \tag{4}$$

The conditions (3) and (4) are necessary to obtain the biological meanings of the state variables x_0, x_1, y_0 and y_1.
In [9], well-posedness of (1), (2) is proved and stability (local and global) of equilibria is investigated. In fact, the disease free equilibrium $E_f = \left(x_0^*, \frac{a_x}{d_1}x_0^*, 0, 0\right)$ is locally asymptotically stable for growth rate of sensitive leukemic stem cells $\gamma > \gamma^* := a_y + \lambda\frac{a_x}{d_1}x_0^*$ and unstable for $\gamma < \gamma^*$ where $x_0^* = \frac{(\beta - a_x)d_1}{\beta_0 d_1 + \lambda a_x}$.
In this paper, we consider the model above including chemotherapeutic treatment. We obtain the following model

$$\dot{x}_0(t) = F_1(x_0, x_1, y_0, y_1), \tag{5}$$
$$\dot{x}_1(t) = F_2(x_0, x_1, y_0, y_1), \tag{6}$$
$$\dot{y}_0(t) = F_3(x_0, x_1, y_0, y_1), \tag{7}$$
$$\dot{y}_1(t) = F_4(x_0, x_1, y_0, y_1), \tag{8}$$

for $t > 0$ and $t \neq t_i$, where t_i is the time of the ith treatment,

$$\begin{aligned} F_1(x_0, x_1, y_0, y_1) &= (\beta - a_x - \beta_0 x_0 - \lambda(x_1 + y_1))x_0, \\ F_2(x_0, x_1, y_0, y_1) &= a_x x_0 - d_1 x_1, \\ F_3(x_0, x_1, y_0, y_1) &= (\gamma - a_y - \gamma_0 y_0 - \lambda(x_1 + \alpha y_1))y_0, \text{ and} \\ F_4(x_0, x_1, y_0, y_1) &= a_y y_0 - d_2 y_1. \end{aligned}$$

For $t = t_i$ we have

$$x_0(t_i^+) = \Theta_1(x_0(t_i), x_1(t_i), y_0(t_i), y_1(t_i)), \tag{9}$$
$$x_1(t_i^+) = \Theta_2(x_0(t_i), x_1(t_i), y_0(t_i), y_1(t_i)), \tag{10}$$
$$y_0(t_i^+) = \Theta_3(x_0(t_i), x_1(t_i), y_0(t_i), y_1(t_i)), \tag{11}$$
$$y_1(t_i^+) = \Theta_4(x_0(t_i), x_1(t_i), y_0(t_i), y_1(t_i)), \tag{12}$$

where $x_j(t_i^+) = \lim_{\substack{t \to t_i \\ t > t_i}} x_j(t)$ and $y_j(t_i^+) = \lim_{\substack{t \to t_i \\ t > t_i}} y_j(t)$, $(j = 0, 1)$ are the size of x_j just after the ith treatment. In our case we have

$$\begin{aligned} \Theta_1(x_0(t_i), x_1(t_i), y_0(t_i), y_1(t_i)) &= x_0(t_i), \\ \Theta_2(x_0(t_i), x_1(t_i), y_0(t_i), y_1(t_i)) &= x_1(t_i), \\ \Theta_3(x_0(t_i), x_1(t_i), y_0(t_i), y_1(t_i)) &= T_0 y_0(t_i), \\ \Theta_4(x_0(t_i), x_1(t_i), y_0(t_i), y_1(t_i)) &= T_1 y_1(t_i). \end{aligned}$$

The variables and parameters are
x_0 : biomass of the normal stem cells,
x_1 : biomass of normal progenitor cells,
y_0 : biomass of sensitive leukemic stem cells,
y_1 : biomass of sensitive leukemic progenitor cells,
β_0 : death rate of the normal stem cells,
γ_0 : death rate of sensitive leukemic stem cells,
β : growth rate of normal stem cells,
γ : growth rate of sensitive leukemic stem cells,
λ : competitive parameter of the stem and progenitor cells,
a_x : produce rate of the normal stem cells,
a_y : produce rate of the sensitive leukemic stem cells,
d_1 : death rate of the normal progenitor cells,
d_2 : death rate of the sensitive leukemic progenitor cells,
α : competition parameter ($0 < \alpha < 1$),

$T_0(< 1)$: survival fraction of sensitive leukemic stem cells,
$T_1(< 1)$: survival fraction of sensitive leukemic progenitor cells, and
τ : is the time of the first treatment, it's the period between two successive injections, that is $t_i = i\tau$, $i \in \mathbf{N}$.
We obtain a special kind of differential equations called impulsive differential equations (see [1]-[6] and [8]).
Our main objective is to study the existence of steady states of (1) and their stability. Our paper is organized as follow ; In the next section we give a mathematical analysis of our model, we study the well-posedness of (1), the existence of the steady states, and the stability of the trivial, chronic, blast and non pathological steady states. Further, we analyze the bifurcation of chronic periodic solutions of (1). Section two is devoted to numerical simulations, in the third section we give some conclusions. The last section is an appendix, where we give calculations needed for the previous sections.

1. Mathematical analysis of the model

1.1. Well-posedness

Theorem 1.1 *The model (5)-(12) has a unique global positive solution for all positive initial conditions*

PROOF. —
Since F_i, $(i = 1, \ldots, 4)$ are smooth, then from the Cauchy-Lipschitz theorem we have the local existence and uniqueness of the solutions of (5)-(8). Since the solutions are bounded then the solution is global in $[0, t_1]$.
The system (5)-(8) is quasi positive because for all x_0, x_1, y_0 and $y_1 \in \mathbf{R}_+$ we have $F_1(0, x_1, y_0, y_1) = 0 \geq 0$, $F_2(x_0, 0, y_0, y_1) = a_x x_0 \geq 0$, $F_3(x_0, x_1, 0, y_1) = 0 \geq 0$ and $F_4(x_0, x_1, y_0, 0) = a_y y_0 \geq 0$, so we have a unique positive global solution in $[0, t_1]$.
By recurrence we can prove that $\forall k \in \mathbf{N}^*$, we have a unique positive global solution in the interval $[t_k, t_{k+1}]$. Hence, we have the existence of a unique positive global solution of (5)-(12).

1.2. Stability of the disease free equilibrium E_f

We can show that $\zeta(t) := \zeta_0 = (\frac{(\beta - a_x)d_1}{\beta_0 d_1 + \lambda a_x}, \frac{\lambda a_x(\beta - a_x)}{\beta_0 d_1 + \lambda a_x}, 0, 0) = E_f$ is a constant equilibrium of (5)-(12), it is called trivial solution.
To study the stability of ζ we use the same approach of fixed point process than in [7] and [11]-[13].
Since solutions of (5)-(8) exist globally in $\mathbf{R}_+$ and are nonnegative (see [9]) we have

$$X(t) = \Phi(t, X_0), t \geq 0 \tag{13}$$

where $X(t) = (x_0, x_1, y_0, y_1)(t)$, $X(0) = X_0$ and Φ is the flow associated to (5)-(12).
The term $X(\tau^+)$ denotes the state of the population after the treatment, $X(\tau^+) = \Theta(X(\tau)) = \Theta(\Phi(\tau, X_0))$.
To have periodic solution we must have $X(\tau^+) = X_0$ that is $X_0 = \Theta(\Phi(\tau, X_0))$.
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 $X = \Phi(., X_0)$ is a τ-periodic solution of (5)-(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 (see [10]).
We need the following hypothesis
$(H1) : a_x < \beta < a_x + \frac{(\beta_0 d_1+\lambda a_x)[(\beta_0 d_1+2\lambda a_x)-2\sqrt{\lambda a_x(\beta_0 d_1+\lambda a_x)}]}{\beta_0^2 d_1}$ or
$\beta > a_x + \frac{(\beta_0 d_1+\lambda a_x)[(\beta_0 d_1+2\lambda a_x)+2\sqrt{\lambda a_x(\beta_0 d_1+\lambda a_x)}]}{\beta_0^2 d_1}$.
We deduce the following results.

Theorem 1.2
Let (H1) be satisfied.

1) If $\gamma \leq \gamma^*$, then the trivial solution ζ is exponentially stable for all $\tau_0 > 0$.

2) If $\gamma > \gamma^*$, then the trivial solution ζ is exponentially stable for $\tau_0 < \tau_0^* := \frac{\ln T_0}{-\gamma+a_y+\lambda\frac{a_x}{d_1}x_0^*}$ and unstable for $\tau_0 > \tau_0^*$.

PROOF. —
We have $D_X\Psi(\tau, X_0) = D_X\Theta(\Phi(\tau, X_0))\dfrac{\partial\Phi}{\partial X}(\tau, X_0)$.
Then, for $X_0 = \zeta_0$ and $\tau = \tau_0$ we have

$$\begin{aligned}
D_X\Psi(\tau_0,\zeta_0) &= D_X\Theta(\Phi(\tau_0,\zeta_0))\tfrac{\partial\Phi}{\partial X}(\tau_0,\zeta_0)\\
&= \begin{pmatrix} 1 & 0 & 0 & 0\\ 0 & 1 & 0 & 0\\ 0 & 0 & T_0 & 0\\ 0 & 0 & 0 & T_1 \end{pmatrix}
\begin{pmatrix} \frac{\partial\Phi_1(\tau_0,\zeta_0)}{\partial x_0} & \frac{\partial\Phi_1(\tau_0,\zeta_0)}{\partial x_1} & \frac{\partial\Phi_1(\tau_0,\zeta_0)}{\partial y_0} & \frac{\partial\Phi_1(\tau_0,\zeta_0)}{\partial y_1}\\ \frac{\partial\Phi_2(\tau_0,\zeta_0)}{\partial x_0} & \frac{\partial\Phi_2(\tau_0,\zeta_0)}{\partial x_1} & 0 & 0\\ 0 & 0 & \frac{\partial\Phi_3(\tau_0,\zeta_0)}{\partial y_0} & 0\\ 0 & 0 & \frac{\partial\Phi_1(\tau_0,\zeta_0)}{\partial y_0} & \frac{\partial\Phi_1(\tau_0,\zeta_0)}{\partial y_1} \end{pmatrix}\\
&= \begin{pmatrix} \frac{\partial\Phi_1(\tau_0,\zeta_0)}{\partial x_0} & \frac{\partial\Phi_1(\tau_0,\zeta_0)}{\partial x_1} & \frac{\partial\Phi_1(\tau_0,\zeta_0)}{\partial y_0} & \frac{\partial\Phi_1(\tau_0,\zeta_0)}{\partial y_1}\\ \frac{\partial\Phi_2(\tau_0,\zeta_0)}{\partial x_0} & \frac{\partial\Phi_2(\tau_0,\zeta_0)}{\partial x_1} & 0 & 0\\ 0 & 0 & T_0\frac{\partial\Phi_3(\tau_0,\zeta_0)}{\partial y_0} & 0\\ 0 & 0 & \frac{\partial\Phi_1(\tau_0,\zeta_0)}{\partial y_0} & T_1\frac{\partial\Phi_1(\tau_0,\zeta_0)}{\partial y_1} \end{pmatrix}.
\end{aligned}$$

The equilibrium ζ is exponentially stable if and only if the spectral radius is less than one.
We have

$$det(D_X\Psi(\tau_0,\zeta_0) - \mu I) = \left(T_0\frac{\partial\Phi_3(\tau_0,\zeta_0)}{\partial y_0} - \mu\right)\left(T_1\frac{\partial\Phi_4(\tau_0,\zeta_0)}{\partial y_1} - \mu\right)\chi(\mu) \tag{16}$$

where

$$\chi(\mu) = \mu^2 - \left(\frac{\partial \Phi_1}{\partial x_0}(\tau_0,\zeta_0) + \frac{\partial \Phi_2}{\partial x_1}(\tau_0,\zeta_0)\right)\mu + \left(\frac{\partial \Phi_1}{\partial x_0}(\tau_0,\zeta_0)\frac{\partial \Phi_2}{\partial x_1}(\tau_0,\zeta_0) - \frac{\partial \Phi_1}{\partial x_1}(\tau_0,\zeta_0)\frac{\partial \Phi_2}{\partial x_0}(\tau_0,\zeta_0)\right). \tag{17}$$

From (16) and (17), the equilibrium $\zeta = E_f$ is exponentially stable if and only if $T_0\left|\frac{\partial \Phi_3}{\partial y_0}(\tau_0,\zeta_0)\right| < 1$, $T_1\left|\frac{\partial \Phi_4}{\partial y_1}(\tau_0,\zeta_0)\right| < 1$ and $|\mu_\pm| < 1$. Where

$$\mu_\pm = \frac{\left(\frac{\partial \Phi_1}{\partial x_0}(\tau_0,\zeta_0) + \frac{\partial \Phi_2}{\partial x_1}(\tau_0,\zeta_0)\right) \pm \sqrt{\Delta}}{2}$$

and

$$\Delta = \left(\frac{\partial \Phi_1}{\partial x_0}(\tau_0,\zeta_0) - \frac{\partial \Phi_2}{\partial x_1}(\tau_0,\zeta_0)\right)^2 + 4\frac{\partial \Phi_1}{\partial x_1}(\tau_0,\zeta_0)\frac{\partial \Phi_2}{\partial x_0}(\tau_0,\zeta_0). \tag{18}$$

From the variational equation $\frac{d}{dt}(D_X\Phi(t,\zeta_0)) = \frac{\partial F}{\partial X}(\zeta_0)\frac{\partial \Phi}{\partial X}(t,\zeta_0)$, we have for all $0 < t \leq \tau_0$

$$\begin{cases} \frac{\partial \Phi_1(t,\zeta_0)}{\partial x_0} &= \frac{d_1+u_2}{u_2-u_1}e^{u_2 t} - \frac{d_1+u_1}{u_2-u_1}e^{u_1 t}, \\ \frac{\partial \Phi_2(t,\zeta_0)}{\partial x_0} &= \frac{a_x}{u_2-u_1}(e^{u_2 t} - e^{u_1 t}), \\ \frac{\partial \Phi_1(t,\zeta_0)}{\partial x_1} &= -\frac{d_1+u_2}{u_2-u_1}\frac{d_1+u_1}{a_x}(e^{u_2 t} - e^{u_1 t}), \\ \frac{\partial \Phi_2(t,\zeta_0)}{\partial x_1} &= -\frac{d_1+u_1}{u_2-u_1}e^{u_2 t} + \frac{d_1+u_2}{u_2-u_1}e^{u_1 t}, \\ \frac{\partial \Phi_3(t,\zeta_0)}{\partial y_0} &= e^{(\gamma - a_y - \lambda\frac{a_x}{d_1}x_0^*)t}, \text{ and} \\ \frac{\partial \Phi_4(t,\zeta_0)}{\partial y_1} &= e^{-d_2 t} \end{cases}$$

where $u_1 = \frac{-\beta x_0^* - d_1 - \sqrt{\Delta_1}}{2} < 0$, $u_2 = \frac{-\beta x_0^* - d_1 + \sqrt{\Delta_1}}{2} < 0$ and $\Delta_1 = (\beta_0 x_0^* - d_1)^2 - 4\lambda a_x x_0^* > 0$ for either

$$0 < \beta - a_x < \frac{(\beta_0 d_1 + \lambda a_x)[(\beta_0 d_1 + 2\lambda a_x) - 2\sqrt{\lambda a_x(\beta_0 d_1 + \lambda a_x)}]}{\beta_0^2 d_1}$$

or

$$\beta - a_x > \frac{(\beta_0 d_1 + \lambda a_x)[(\beta_0 d_1 + 2\lambda a_x) + 2\sqrt{\lambda a_x(\beta_0 d_1 + \lambda a_x)}]}{\beta_0^2 d_1}$$

(see Appendix, Subsection 4.1).

Then, we obtain $\Delta = \left(e^{u_2 t} - e^{u_1 t}\right)^2$, $\mu_- = e^{u_1 \tau_0} \in (0,1)$ and $\mu_+ = e^{u_2 \tau_0} \in (0,1)$.

REMARK. —

1) In the hypothesis (H1), the condition $\beta > a_x$ is a biological condition, which will allow the preservation of the population of healthy hematopoietic stem cells. On the other hand, $\beta < a_x + \frac{(\beta_0 d_1 + \lambda a_x)[(\beta_0 d_1 + 2\lambda a_x) - 2\sqrt{\lambda a_x(\beta_0 d_1 + \lambda a_x)}]}{\beta_0^2 d_1}$ and $\beta > a_x + \frac{(\beta_0 d_1 + \lambda a_x)[(\beta_0 d_1 + 2\lambda a_x) + 2\sqrt{\lambda a_x(\beta_0 d_1 + \lambda a_x)}]}{\beta_0^2 d_1}$ are technical conditions which will make it possible to determine the stability of the periodic solutions without diseases.

2) If (H1) is satisfied and $\gamma > \gamma^*$ we have $T_1\left|\frac{\partial \Phi_4}{\partial y_1}(\tau_0,\zeta_0)\right| < 1$ for $\tau_0 < \tau_0^*$ and

$T_0 \left| \frac{\partial \Phi_3}{\partial y_0}(\tau_0, \zeta_0) \right| = 1$ for $\tau_0 = \tau_0^*$. That is we have a critical case at $\tau_0 = \tau_0^*$.
3) From theorem 1.2, if (H1) is satisfied we show that in case of low growth rate of leukemic sensitive stem cells $\gamma(\leq \gamma^*)$ we can choose any period τ_0 of treatment to have eradication of the disease. Otherwise, for high growth rate of leukemic sensitive stem cells $\gamma(> \gamma^*)$, the eradication of the disease is acquired only for period τ_0 less than some threshold τ_0^*.

1.3. Bifurcation Analysis of nontrivial periodic solution

In this subsection, we analyze the bifurcation of nontrivial periodic solutions of $(5)-(12)$ from ζ at $\tau_0 = \tau_0^*$. This case is possible if $(H1)$ is satisfied and $\gamma > \gamma^*$ (see theorem 1.2). The bifurcated solutions means that the disease is installed.
Let $\bar{\tau}$ and $\bar{X}$ such that $\tau = \tau_0^* + \bar{\tau}$ and $X = \zeta_0 + \bar{X}$. The equation (15) is equivalent to

$$M(\bar{\tau}, \bar{X}) = 0, \tag{19}$$

where $M(\bar{\tau}, \bar{X}) = \big(M_1(\bar{\tau}, \bar{X}), \ldots, M_4(\bar{\tau}, \bar{X})\big) := \zeta_0 + \bar{X} - \Psi(\tau_0 + \bar{\tau}, \zeta_0 + \bar{X})$.
If $(\bar{\tau}, \bar{X})$ is a zero of M, then $(\zeta_0 + \bar{X})$ is a fixed point of $\Psi(\tau_0^* + \bar{\tau}, .)$. Let

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

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

$$\begin{aligned} D_X M(0,(0,0,0,0)) &= \begin{pmatrix} a_0 & b_0 & c_0 & d_0 \\ e_0 & f_0 & \star & \star \\ \star & \star & g_0 & \star \\ \star & \star & h_0 & i_0 \end{pmatrix} \\ &= \begin{pmatrix} 1 - \frac{\partial \Phi_1}{\partial x_0} & -\frac{\partial \Phi_1}{\partial x_1} & -\frac{\partial \Phi_1}{\partial y_0} & -\frac{\partial \Phi_1}{\partial y_1} \\ -\frac{\partial \Phi_2}{\partial x_0} & 1 - \frac{\partial \Phi_2}{\partial x_1} & 0 & 0 \\ 0 & 0 & 1 - T_0 \frac{\partial \Phi_3}{\partial y_0} & 0 \\ 0 & 0 & -T_1 \frac{\partial \Phi_4}{\partial y_0} & 1 - T_1 \frac{\partial \Phi_4}{\partial y_1} \end{pmatrix} (\tau_0^*, \zeta_0). \end{aligned}$$

Then $a_0 = 1 - \frac{\partial \Phi_1}{\partial x_0}(\tau_0^*, \zeta_0)$, $b_0 = -\frac{\partial \Phi_1}{\partial x_1}(\tau_0^*, \zeta_0)$, $c_0 = -\frac{\partial \Phi_1}{\partial y_0}(\tau_0^*, \zeta_0)$, $d_0 = -\frac{\partial \Phi_1}{\partial y_1}$, $e_0 = -\frac{\partial \Phi_2}{\partial x_0}(\tau_0^*, \zeta_0)$,

$f_0 = 1 - \frac{\partial \Phi_2}{\partial x_1}(\tau_0^*, \zeta_0)$, $g_0 = 1 - T_0 \frac{\partial \Phi_3}{\partial y_0}(\tau_0^*, \zeta_0)$, $h_0 = -T_1 \frac{\partial \Phi_4}{\partial y_0}(\tau_0^*, \zeta_0)$ and $i_0 = 1 - T_1 \frac{\partial \Phi_4}{\partial y_1}(\tau_0^*, \zeta_0)$.
We have the critical cases if and only if $\det D_X M(0,(0,0,0,0)) = (a_0 f_0 - b_0 e_0) g_0 i_0 = 0$. That is

$$g_0 = 0 \tag{21}$$

since $i_0 = 1 - T_1 e^{-d_2 \tau_0^*} \in (0,1)$ and $a_0 f_0 - b_0 e_0 = (1 - e^{u_2 \tau_0^*})(1 - e^{u_1 \tau_0^*}) \in (0,1)$.
We have $M(0,(0,0,0,0)) = 0$. Let $D_X M(0,(0,0,0,0)) = E$, then $\dim \ker(E) = \operatorname{co}\dim \mathcal{R}(\mathrm{E}) = 1$. Denote by P_1 and P_2 the projectors onto $\ker(E)$ and $\mathcal{R}(E)$ respectively, such that $P_1 + P_2 = Id_{\mathbf{R}^4}$, $P_1 \mathbf{R}^4 = \operatorname{span}\{\mathrm{Y}_0\} = \ker(\mathrm{E})$, with $Y_0 = (q_1, q_2, 1, q_4)$, $q_1 = \frac{f_0(c_0 i_0 - d_0 h_0)}{i_0(b_0 e_0 - a_0 f_0)}$, $q_2 = -\frac{e_0(c_0 i_0 - d_0 h_0)}{i_0(b_0 e_0 - a_0 f_0)}$, $q_4 = \frac{-h_0}{i_0}$ and
$P_2 \mathbf{R}^4 = \operatorname{span}\{(1,0,0,0),(0,1,0,0),(0,0,0,1)\} = \mathcal{R}(E)$.
Then $(I - P_1)\mathbf{R}^4 = \operatorname{span}\{(1,0,0,0),(0,1,0,0),(0,0,0,1)\}$ and
$(I - P_2)\mathbf{R}^4 = \operatorname{span}\{(0,0,1,0)\}$.
Equation (19) is equivalent to

$$\begin{cases} M_1(\bar{\tau}, \sigma Y_0 + Z) &= 0, \\ M_2(\bar{\tau}, \sigma Y_0 + Z) &= 0, \\ M_3(\bar{\tau}, \sigma Y_0 + Z) &= 0, \\ M_4(\bar{\tau}, \sigma Y_0 + Z) &= 0, \end{cases} \tag{22}$$

where $Z = (z_1, z_2, 0, z_4)$, $(\bar{\tau}, \bar{X}) = (\bar{\tau}, \sigma Y_0 + Z)$ and $(\sigma, z_1, z_2, z_4) \in \mathbf{R}^4$.
From the three equations of (22), we have

$$\begin{aligned} \det \begin{pmatrix} \frac{\partial M_1(0,(0,0,0,0))}{\partial z_1} & \frac{\partial M_1(0,(0,0,0,0))}{\partial z_2} & \frac{\partial M_1(0,(0,0,0,0))}{\partial z_4} \\ \frac{\partial M_2(0,(0,0,0,0))}{\partial z_1} & \frac{\partial M_2(0,(0,0,0,0))}{\partial z_2} & \frac{\partial M_2(0,(0,0,0,0))}{\partial z_4} \\ \frac{\partial M_4(0,(0,0,0,0))}{\partial z_1} & \frac{\partial M_4(0,(0,0,0,0))}{\partial z_2} & \frac{\partial M_4(0,(0,0,0,0))}{\partial z_4} \end{pmatrix} &= \det \begin{pmatrix} a_0 & b_0 & d_0 \\ e_0 & f_0 & 0 \\ 0 & 0 & i_0 \end{pmatrix} \\ &= i_0(a_0 f_0 - e_0 b_0) \neq 0. \end{aligned}$$

From the implicit function theorem, there exist a unique continuous function Z^*, such that
$Z^*(\bar{\tau}, \sigma) = (z_1^*(\bar{\tau}, \sigma), z_2^*(\bar{\tau}, \sigma), 0, z_4^*(\bar{\tau},))$, $Z^*(0,0) = (0,0,0,0)$ and

$$M_i\left(\bar{\tau}, (q_1 \sigma + z_1^*(\bar{\tau}, \sigma), q_2 \sigma + z_2^*(\bar{\tau}, \sigma), \sigma, q_4 \sigma + z_4^*(\bar{\tau}, \sigma))\right) = 0, \tag{23}$$

for $i = 1,\ 2,\ 4$, with σ and $\bar{\tau}$ small enough.
We have $\dfrac{\partial Z^*}{\partial \bar{\tau}}(0,0) = 0$ and $\frac{\partial Z^*}{\partial \sigma}(0,0) = (-\frac{f_0 c_0}{a_0 f_0 - e_0 b_0}, \frac{c_0 e_0}{a_0 f_0 - e_0 b_0}, 0, 0)$ (see Appendix, subsection 4.3).
We have the following theorem.

Theorem 1.3 *Let (H1) be satisfied and $\gamma > \gamma^*$. There exist $\lambda_0 > 0$ such that for $\lambda \in (0, \lambda_0)$ we have a supercritical bifurcation of nontrivial periodic solutions of (5)-(12) with period $\tau(\sigma) = \tau_0^* + \bar{\tau}(\sigma)$ starting from $\zeta_0 + \sigma Y_0 + Z^*(\bar{\tau}(\sigma), \sigma)$ for $\sigma (> 0)$ small enough where $\bar{\tau}(\sigma) = -\frac{\mathcal{C}}{2\mathcal{B}}\sigma + \circ(\sigma)$.*

PROOF. —
We have $M(\bar{\tau}, \bar{X}) = 0$ if and only if

$$\omega(\bar{\tau}, \sigma) = M_3\left(\bar{\tau}, (q_1 \sigma + z_1^*(\bar{\tau}, \sigma), q_2 \sigma + z_2^*(\bar{\tau}, \sigma), \sigma, q_4 \sigma + z_4^*(\bar{\tau}, \sigma))\right) = 0. \tag{24}$$

We find $\omega(0,0)=0$ and $\frac{\partial\omega(0,0)}{\partial\bar{\tau}}=\frac{\partial\omega(0,0)}{\partial\sigma}=0$ (see Appendix, subsection 4.4).
Let $\mathcal{A}=\frac{\partial^2\omega(0,0)}{\partial\bar{\tau}^2}$, $\mathcal{B}=\frac{\partial^2\omega(0,0)}{\partial\bar{\tau}\partial\sigma}$ and $\mathcal{C}=\frac{\partial^2\omega(0,0)}{\partial\sigma^2}$. It's shown that $\mathcal{A}=0$ (see Appendix, subsection 4.5). Hence

$$\omega(\bar{\tau},\sigma)=\mathcal{B}\bar{\tau}\sigma+\mathcal{C}\frac{\sigma^2}{2}+o\left(|\sigma|^2+|\bar{\tau}|^2\right),$$

where

$$\begin{aligned}\mathcal{B} &= -\frac{\partial\Theta_3}{\partial y_0}\frac{\partial^2\Phi_3(\tau_0,\zeta_0)}{\partial\bar{\tau}\partial y_0}\\ &= -(\gamma-a_y-\lambda\tfrac{a_x}{d_1}x_0^*)<0\end{aligned}$$

and

$$\begin{aligned}\mathcal{C} &= -\frac{\partial\Theta_3}{\partial y_0}\left\{2\frac{\partial^2\Phi_3(\tau_0,\zeta_0)}{\partial x_0\partial y_0}\left(q_1+\frac{\partial z_1^*(0,0)}{\partial\sigma}\right)+2\frac{\partial^2\Phi_3(\tau_0,\zeta_0)}{\partial x_1\partial y_0}\left(q_2+\frac{\partial z_2^*(0,0)}{\partial\sigma}\right)\right.\\ &\quad\left.+2\frac{\partial^2\Phi_3(\tau_0,\zeta_0)}{\partial y_0\partial y_1}q_4+\frac{\partial^2\Phi_3(\tau_0,\zeta_0)}{\partial y_0^2}\right\}\\ &= 2\lambda\frac{a_x}{u_2-u_1}\left(\frac{e^{u_2\tau_0}-1}{u_2}-\frac{e^{u_1\tau_0}-1}{u_1}\right)\frac{f_0(d_0h_0-2c_0i_0)}{i_0(a_0f_0-b_0e_0)}\\ &\quad+2\lambda\left(\frac{d_1+u_2}{u_2-u_1}\left(\frac{e^{u_2\tau_0}-1}{u_2}\right)-\frac{d_1+u_1}{u_2-u_1}\left(\frac{e^{u_1\tau_0}-1}{u_1}\right)\right)\frac{e_0(d_0h_0-2c_0i_0)}{i_0(a_0f_0-b_0e_0)}\\ &\quad+2\lambda\alpha\left(\frac{e^{-d_2\tau_0}-1}{d_2}\right)\frac{h_0}{i_0}+2\gamma_0\left(\frac{e^{(\gamma-a_y-\lambda\frac{a_x}{d_1}x_0^*)\tau_0}-1}{\gamma-a_y-\lambda\frac{a_x}{d_1}x_0^*}\right)\\ &\quad+\lambda\alpha\frac{a_y}{\gamma-a_y-\lambda\frac{a_x}{d_1}x_0^*+d_2}\left(\frac{e^{(\gamma-a_y-\lambda\frac{a_x}{d_1}x_0^*)\tau_0}-1}{\gamma-a_y-\lambda\frac{a_x}{d_1}x_0^*}+\frac{e^{-d_2\tau_0}-1}{d_2}\right).\end{aligned}$$

For $\lambda=0$, we have

$$\mathcal{C} = 2\gamma_0\left(\frac{e^{(\gamma-a_y)\tau_0}-1}{\gamma-a_y}\right)>0.$$

REMARK. —
From theorem 1.3, we deduce that for high growth rate of leukemic sensitive stem cells $\gamma(>\gamma^*)$ and period of treatment dose $\tau_0=\tau_0^*$ there is lost of stability of the disease free equilibrium and we note the presence of nontrivial periodic solution which means that the disease is installed for period $\tau_0(\sigma)$ close to τ_0^*.

2. Numerical simulations

To illustrate our results, we give some numerical simulations.

In Figure 1, we consider the case of the theorem 1.2, we have the stability of the healthy steady state E_f.

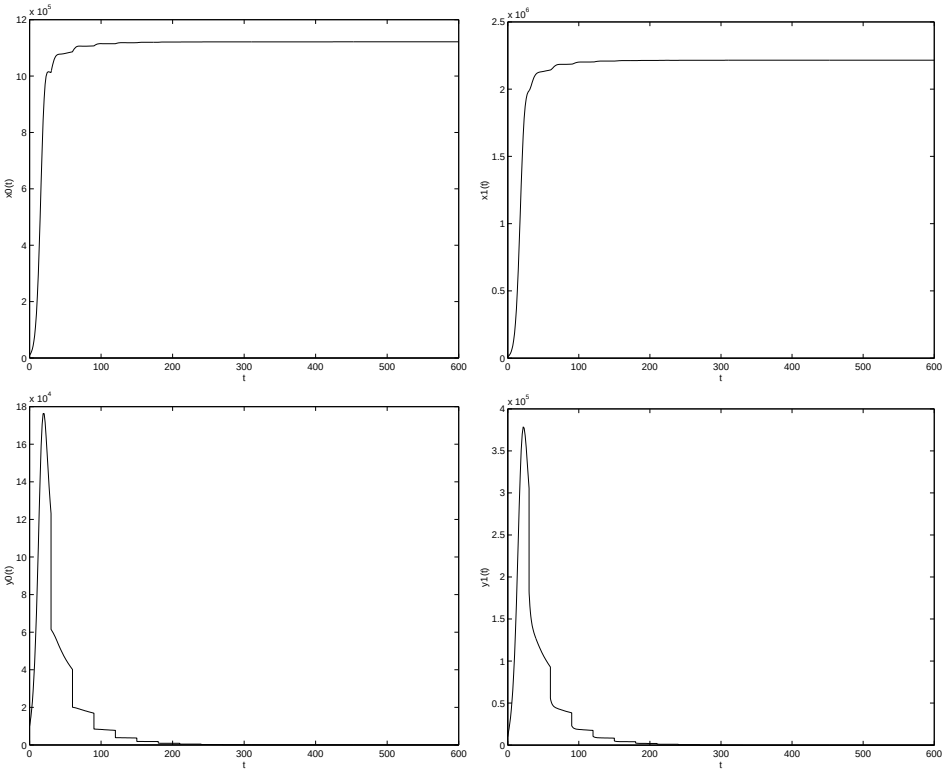

Figure 1. *The curves of normal stem cells (top left), normal progenitor cells (top right), leukemic stem cells (bottom left) and leukemic progenitor cells (bottom right) with* $\beta = 1.1$, $a_x = 0.8$, $\beta_0 = 0.00000007$, $\lambda = 0.0000001$, $d_1 = 0.405$, $\gamma = 1.121$, $a_y = 0.9$, $\gamma_0 = 0.0000003$, $\alpha = 0.8$, $d_2 = 0.402$, $T_0 = 0.5$, $T_1 = 0.6$, $\tau = 30$, $x_0(0) = 10000$, $x_1(0) = 10000$, $y_0(0) = 10000$ *and* $y_1(0) = 10000$

In the Figure 2, we consider the case of the theorem 1.2, we have the instability of the healthy steady state E_f, we see that leukemic cells reappears.

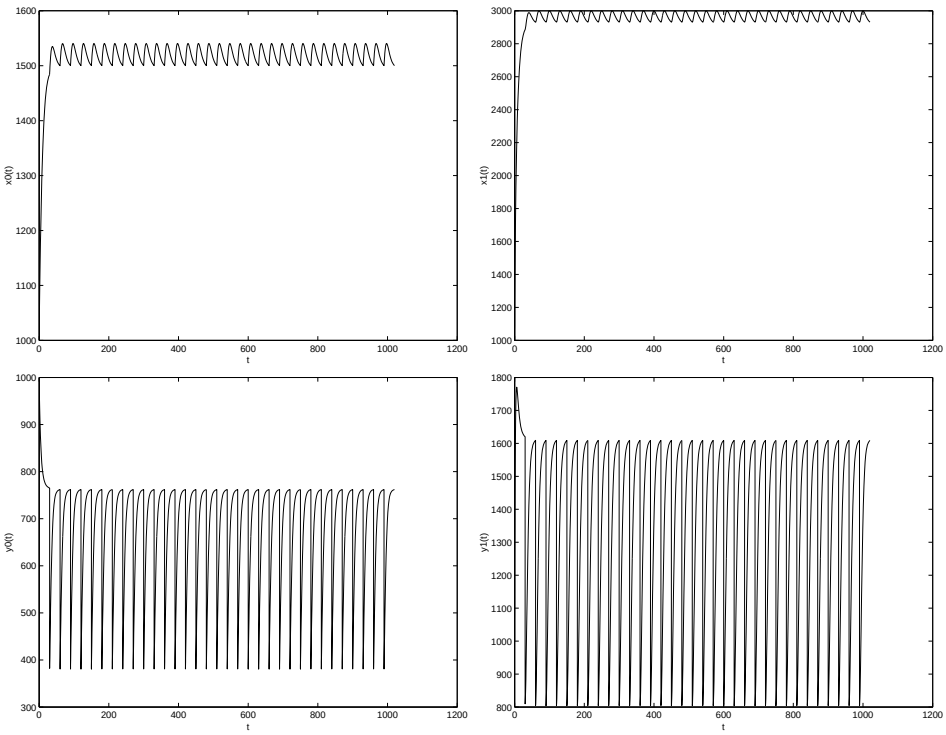

Figure 2. *The curves of normal stem cells (top left), normal progenitor cells (top right), leukemic stem cells (bottom left) and leukemic progenitor cells (bottom right) with* $\beta = 0.95$, $a_x = 0.8$, $\beta_0 = 0.00007$, $\lambda = 0.0001$, $d_1 = 0.41$, $\gamma = 1.121$, $a_y = 0.85$, $\gamma_0 = 0.0003$, $\alpha = 0.8$, $d_2 = 0.402$, $T_0 = 0.5$, $T_1 = 0.5$, $\tau = 30$, $x_0(0) = 1000$, $x_1(0) = 1000$, $y_0(0) = 1000$ *and* $y_1(0) = 1000$

In Figure 3, we consider the case of the theorem 1.3, we have the bifurcation of periodic solutions for the treatment period $\tau = \tau_0^*$.

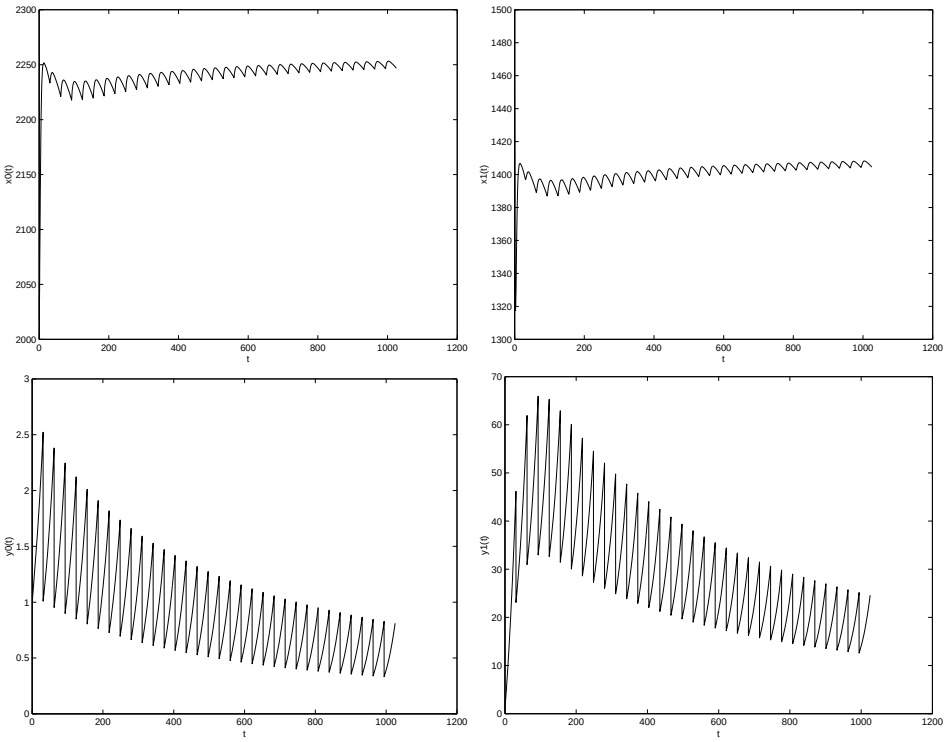

Figure 3. *The curves of normal stem cells (top left), normal progenitor cells (top right), leukemic stem cells (bottom left) and leukemic progenitor cells (bottom right) with* $\beta = 0.8$, $a_x = 0.5$, $\beta_0 = 0.00007$, $\lambda = 0.0001$, $d_1 = 0.8$, $\gamma = 1.121$, $a_y = 0.95$, $\gamma_0 = 0.0003$, $\alpha = 0.8$, $d_2 = 0.007$, $T_0 = 0.4$, $T_1 = 0.5$, $\tau = \tau_0^* = 31.0706$, $x_0(0) = 2000$, $x_1(0) = 1500$, $y_0(0) = 1$ *and* $y_1(0) = 1$

3. Conclusions

In this work we have analyzed a mathematical model of chronic myeloid leukemia (CML) which is an extension of a model developed in [9] in the case without medical treatment. In our work, we considered the case of a treatment with instantaneous effect described by discrete equations called impulses. We have studied the stability of the healthy equilibrium (trivial solution), it becomes stable if the growth rate of resistant stem cells γ does not exceed a certain threshold γ^*, if it reaches this threshold we obtain a critical case which gives bifurcations what we want say that is the tumor persists and remains viable.

4. Appendix

4.1. First derivatives of Φ

For all $t \in (0, \tau]$, we have $\frac{d}{dt} D_X(\Phi(t, \zeta_0)) = \frac{\partial F}{\partial X}(\zeta_0) \frac{\partial \Phi}{\partial X}(t, \zeta_0)$ with the initial condition $D_X(\Phi(0, \zeta_0)) = I_{\mathbf{R}^4}$, where

$$\frac{d}{dt} D_X(\Phi(t, \zeta_0)) = \frac{d}{dt} \begin{pmatrix} \frac{\partial \Phi_1(t,\zeta_0)}{\partial x_0} & \frac{\partial \Phi_1(t,\zeta_0)}{\partial x_1} & \frac{\partial \Phi_1(t,\zeta_0)}{\partial y_0} & \frac{\partial \Phi_1(t,\zeta_0)}{\partial y_1} \\ \frac{\partial \Phi_2(t,\zeta_0)}{\partial x_0} & \frac{\partial \Phi_2(t,\zeta_0)}{\partial x_1} & \frac{\partial \Phi_2(t,\zeta_0)}{\partial y_0} & \frac{\partial \Phi_2(t,\zeta_0)}{\partial y_1} \\ \frac{\partial \Phi_3(t,\zeta_0)}{\partial x_0} & \frac{\partial \Phi_3(t,\zeta_0)}{\partial x_1} & \frac{\partial \Phi_3(t,\zeta_0)}{\partial y_0} & \frac{\partial \Phi_3(t,\zeta_0)}{\partial y_1} \\ \frac{\partial \Phi_4(t,\zeta_0)}{\partial x_0} & \frac{\partial \Phi_4(t,\zeta_0)}{\partial x_1} & \frac{\partial \Phi_4(t,\zeta_0)}{\partial y_0} & \frac{\partial \Phi_4(t,\zeta_0)}{\partial y_1} \end{pmatrix},$$

$$\begin{aligned} \frac{\partial F}{\partial X}(\zeta_0) &= \begin{pmatrix} \frac{\partial F_1(\zeta(t))}{\partial x_0} & \frac{\partial F_1(\zeta(t))}{\partial x_1} & \frac{\partial F_1(\zeta(t))}{\partial y_0} & \frac{\partial F_1(\zeta(t))}{\partial y_1} \\ \frac{\partial F_2(\zeta(t))}{\partial x_0} & \frac{\partial F_2(\zeta(t))}{\partial x_1} & \frac{\partial F_2(\zeta(t))}{\partial y_0} & \frac{\partial F_2(\zeta(t))}{\partial y_1} \\ \frac{\partial F_3(\zeta(t))}{\partial x_0} & \frac{\partial F_3(\zeta(t))}{\partial x_1} & \frac{\partial F_3(\zeta(t))}{\partial y_0} & \frac{\partial F_3(\zeta(t))}{\partial y_1} \\ \frac{\partial F_4(\zeta(t))}{\partial x_0} & \frac{\partial F_4(\zeta(t))}{\partial x_1} & \frac{\partial F_4(\zeta(t))}{\partial y_0} & \frac{\partial F_4(\zeta(t))}{\partial y_1} \end{pmatrix} \\ &= \begin{pmatrix} -\beta_0 x_0^* & -\lambda x_0^* & 0 & -\lambda x_0^* \\ a_x & -d_1 & 0 & 0 \\ 0 & 0 & \gamma - a_y - \lambda \frac{a_x}{d_1} x_0^* & 0 \\ 0 & 0 & a_y & -d_2 \end{pmatrix}, \end{aligned}$$

and

$$\frac{\partial \Phi}{\partial X}(t, \zeta_0) = \begin{pmatrix} \frac{\partial \Phi_1(t,\zeta_0)}{\partial x_0} & \frac{\partial \Phi_1(t,\zeta_0)}{\partial x_1} & \frac{\partial \Phi_1(t,\zeta_0)}{\partial y_0} & \frac{\partial \Phi_1(t,\zeta_0)}{\partial y_1} \\ \frac{\partial \Phi_2(t,\zeta_0)}{\partial x_0} & \frac{\partial \Phi_2(t,\zeta_0)}{\partial x_1} & \frac{\partial \Phi_2(t,\zeta_0)}{\partial y_0} & \frac{\partial \Phi_2(t,\zeta_0)}{\partial y_1} \\ \frac{\partial \Phi_3(t,\zeta_0)}{\partial x_0} & \frac{\partial \Phi_3(t,\zeta_0)}{\partial x_1} & \frac{\partial \Phi_3(t,\zeta_0)}{\partial y_0} & \frac{\partial \Phi_3(t,\zeta_0)}{\partial y_1} \\ \frac{\partial \Phi_4(t,\zeta_0)}{\partial x_0} & \frac{\partial \Phi_4(t,\zeta_0)}{\partial x_1} & \frac{\partial \Phi_4(t,\zeta_0)}{\partial y_0} & \frac{\partial \Phi_4(t,\zeta_0)}{\partial y_1} \end{pmatrix}.$$

From Cauchy Lipschitz theorem (uniqueness of solution) we obtain that $\frac{\partial \Phi_2(t,\zeta_0)}{\partial y_i} = \frac{\partial \Phi_3(t,\zeta_0)}{\partial x_i} = \frac{\partial \Phi_4(t,\zeta_0)}{\partial x_i} = 0,\ i \in \{0,\ 1\}$ and $\frac{\partial \Phi_3(t,\zeta_0)}{\partial y_1} = 0$. Moreover, we have

$$\frac{d}{dt}\left(\frac{\partial \Phi_1(t,\zeta_0)}{\partial x_0}\right) = \frac{\partial F_1(\zeta(t))}{\partial x_0} \frac{\partial \Phi_1(t,\zeta_0)}{\partial x_0} + \frac{\partial F_1(\zeta(t))}{\partial x_1} \frac{\partial \Phi_2(t,\zeta_0)}{\partial x_0}, \tag{25}$$

$$\frac{d}{dt}\left(\frac{\partial \Phi_1(t,\zeta_0)}{\partial x_1}\right) = \frac{\partial F_1(\zeta(t))}{\partial x_0} \frac{\partial \Phi_1(t,\zeta_0)}{\partial x_1} + \frac{\partial F_1(\zeta(t))}{\partial x_1} \frac{\partial \Phi_2(t,\zeta_0)}{\partial x_1}, \tag{26}$$

$$\frac{d}{dt}\left(\frac{\partial \Phi_1(t,\zeta_0)}{\partial y_0}\right) = \frac{\partial F_1(\zeta(t))}{\partial x_0} \frac{\partial \Phi_1(t,\zeta_0)}{\partial y_0} + \frac{\partial F_1(\zeta(t))}{\partial y_1} \frac{\partial \Phi_4(t,\zeta_0)}{\partial y_0}, \tag{27}$$

$$\frac{d}{dt}\left(\frac{\partial \Phi_1(t,\zeta_0)}{\partial y_1}\right) = \frac{\partial F_1(\zeta(t))}{\partial x_0} \frac{\partial \Phi_1(t,\zeta_0)}{\partial y_1} + \frac{\partial F_1(\zeta(t))}{\partial y_1} \frac{\partial \Phi_4(t,\zeta_0)}{\partial y_1}, \tag{28}$$

$$\frac{d}{dt}\left(\frac{\partial \Phi_2(t,\zeta_0)}{\partial x_0}\right) = \frac{\partial F_2(\zeta(t))}{\partial x_0} \frac{\partial \Phi_1(t,\zeta_0)}{\partial x_0} + \frac{\partial F_2(\zeta(t))}{\partial x_1} \frac{\partial \Phi_2(t,\zeta_0)}{\partial x_0}, \tag{29}$$

$$\frac{d}{dt}\left(\frac{\partial \Phi_2(t,\zeta_0)}{\partial x_1}\right) = \frac{\partial F_2(\zeta(t))}{\partial x_0} \frac{\partial \Phi_1(t,\zeta_0)}{\partial x_1} + \frac{\partial F_2(\zeta(t))}{\partial x_1} \frac{\partial \Phi_2(t,\zeta_0)}{\partial x_1}, \tag{30}$$

$$\frac{d}{dt}\left(\frac{\partial \Phi_3(t,\zeta_0)}{\partial y_0}\right) = \frac{\partial F_3(\zeta(t))}{\partial y_0} \frac{\partial \Phi_3(t,\zeta_0)}{\partial y_0}, \tag{31}$$

$$\frac{d}{dt}\left(\frac{\partial \Phi_4(t,\zeta_0)}{\partial y_0}\right) = \frac{\partial F_4(\zeta(t))}{\partial y_0} \frac{\partial \Phi_3(t,\zeta_0)}{\partial y_0} + \frac{\partial F_4(\zeta(t))}{\partial y_1} \frac{\partial \Phi_4(t,\zeta_0)}{\partial y_0}, \tag{32}$$

$$\frac{d}{dt}\left(\frac{\partial\Phi_4(t,\zeta_0)}{\partial y_1}\right) = \frac{\partial F_4(\zeta(t))}{\partial y_1}\frac{\partial\Phi_4(t,\zeta_0)}{\partial y_1}. \tag{33}$$

From (31) we obtain $\frac{\partial\Phi_3(t,\zeta_0)}{\partial y_0} = e^{(\gamma-a_y-\lambda\frac{a_x}{d_1}x_0^*)t}$.
From (32) we obtain $\frac{\partial\Phi_4(t,\zeta_0)}{\partial y_0} = \frac{a_y}{\gamma-a_y-\lambda\frac{a_x}{d_1}x_0^*+d_2}(e^{(\gamma-a_y-\lambda\frac{a_x}{d_1}x_0^*)t} - e^{-d_2t})$.
From (33) we have $\frac{\partial\Phi_4(t,\zeta_0)}{\partial y_1} = e^{-d_2t}$.
From (25) and (29) we have $\begin{pmatrix} \frac{\partial\Phi_1(t,\zeta_0)}{\partial x_0} \\ \frac{\partial\Phi_2(t,\zeta_0)}{\partial x_0} \end{pmatrix} = e^{tA}\begin{pmatrix} \frac{\partial\Phi_1(0,\zeta_0)}{\partial x_0} \\ \frac{\partial\Phi_2(0,\zeta_0)}{\partial x_0} \end{pmatrix} = e^{tA}\begin{pmatrix} 1 \\ 0 \end{pmatrix}$, where

$$A = \begin{pmatrix} \frac{\partial F_1(\zeta(t))}{\partial x_0} & \frac{\partial F_1(\zeta(t))}{\partial x_1} \\ \frac{\partial F_2(\zeta(t))}{\partial x_0} & \frac{\partial F_2(\zeta(t))}{\partial x_1} \end{pmatrix} = \begin{pmatrix} -\beta_0 x_0^* & -\lambda x_0^* \\ a_x & -d_1 \end{pmatrix} = PVP^{-1},\ V = \begin{pmatrix} u_1 & 0 \\ 0 & u_2 \end{pmatrix},$$

$$P = \begin{pmatrix} \frac{d_1+u_1}{a_x} & \frac{d_1+u_2}{a_x} \\ 1 & 1 \end{pmatrix},\ P^{-1} = \begin{pmatrix} -\frac{a_x}{u_2-u_1} & \frac{d_1+u_2}{u_2-u_1} \\ \frac{a_x}{u_2-u_1} & -\frac{d_1+u_1}{u_2-u_1} \end{pmatrix},$$

where $u_1 = \frac{\beta x_0^*+d_1-\sqrt{\Delta}}{2}$, $u_2 = \frac{\beta x_0^*+d_1+\sqrt{\Delta}}{2}$, $\Delta = (\beta_0 x_0^* - d_1)^2 - 4\lambda a_x x_0^*$ and

$$\begin{aligned} e^{tA} &= Pe^{tV}P^{-1} \\ &= \begin{pmatrix} \frac{d_1+u_1}{a_x} & \frac{d_1+u_2}{a_x} \\ 1 & 1 \end{pmatrix}\begin{pmatrix} e^{u_1t} & 0 \\ 0 & e^{u_2t} \end{pmatrix}\begin{pmatrix} -\frac{a_x}{u_2-u_1} & \frac{d_1+u_2}{u_2-u_1} \\ \frac{a_x}{u_2-u_1} & -\frac{d_1+u_1}{u_2-u_1} \end{pmatrix} \\ &= \begin{pmatrix} \frac{d_1+u_1}{a_x}e^{u_1t} & \frac{d_1+u_2}{a_x}e^{u_2t} \\ e^{u_1t} & e^{u_2t} \end{pmatrix}\begin{pmatrix} -\frac{a_x}{u_2-u_1} & \frac{d_1+u_2}{u_2-u_1} \\ \frac{a_x}{u_2-u_1} & -\frac{d_1+u_1}{u_2-u_1} \end{pmatrix} \\ &= \begin{pmatrix} \frac{d_1+u_2}{u_2-u_1}e^{u_2t} - \frac{d_1+u_1}{u_2-u_1}e^{u_1t} & -\frac{d_1+u_2}{u_2-u_1}\frac{d_1+u_1}{a_x}(e^{u_2t}-e^{u_1t}) \\ \frac{a_x}{u_2-u_1}(e^{u_2t}-e^{u_1t}) & -\frac{d_1+u_1}{u_2-u_1}e^{u_2t} + \frac{d_1+u_2}{u_2-u_1}e^{u_1t} \end{pmatrix}. \end{aligned}$$

We obtain

$$\begin{cases} \frac{\partial\Phi_1(t,\zeta_0)}{\partial x_0} &= \frac{d_1+u_2}{u_2-u_1}e^{u_2t} - \frac{d_1+u_1}{u_2-u_1}e^{u_1t}, \\ \frac{\partial\Phi_2(t,\zeta_0)}{\partial x_0} &= \frac{a_x}{u_2-u_1}(e^{u_2t}-e^{u_1t}). \end{cases}$$

From (26) and (30) we have $\begin{pmatrix} \frac{\partial\Phi_1(t,\zeta_0)}{\partial x_1} \\ \frac{\partial\Phi_2(t,\zeta_0)}{\partial x_1} \end{pmatrix} = e^{tA}\begin{pmatrix} \frac{\partial\Phi_1(0,\zeta_0)}{\partial x_1} \\ \frac{\partial\Phi_2(0,\zeta_0)}{\partial x_1} \end{pmatrix} = e^{tA}\begin{pmatrix} 0 \\ 1 \end{pmatrix}$. We obtain

$$\begin{cases} \frac{\partial\Phi_1(t,\zeta_0)}{\partial x_1} &= -\frac{d_1+u_2}{u_2-u_1}\frac{d_1+u_1}{a_x}(e^{u_2t}-e^{u_1t}), \\ \frac{\partial\Phi_2(t,\zeta_0)}{\partial x_1} &= -\frac{d_1+u_1}{u_2-u_1}e^{u_2t} + \frac{d_1+u_2}{u_2-u_1}e^{u_1t}. \end{cases}$$

From (27) we have

$$\frac{\partial\Phi_1(t,\zeta_0)}{\partial y_0} = -\frac{\lambda a_y x_0^* e^{-\beta_0 x_0^* t}}{\gamma - a_y - \lambda\frac{a_x}{d_1}x_0^* + d_2}\left(\frac{e^{(\gamma-a_y-\lambda\frac{a_x}{d_1}x_0^*+\beta_0x_0^*)t}-1}{\gamma-a_y-\lambda\frac{a_x}{d_1}x_0^*+\beta_0x_0^*} - \frac{e^{(\beta_0x_0^*-d_2)t}-1}{\beta_0x_0^*-d_2}\right),$$

From (28) we have

$$\frac{\partial\Phi_1(t,\zeta_0)}{\partial y_1} = -\lambda x_0^* e^{-\beta_0 x_0^* t}\left(\frac{e^{(\beta_0x_0^*-d_2)t}-1}{\beta_0x_0^*-d_2}\right).$$

4.2. Second derivatives of Φ_3

The second partial derivatives of Φ_3 can be obtained from the following differential equations,

$$\begin{aligned}
\frac{d}{dt}\left(\frac{\partial^2\Phi_3(t,\zeta_0)}{\partial x_0^2}\right) &= \frac{\partial F_3(\zeta(t))}{\partial x_0}\frac{\partial^2\Phi_1(t,\zeta_0)}{\partial x_0^2} + \frac{\partial F_3(\zeta(t))}{\partial x_1}\frac{\partial^2\Phi_2(t,\zeta_0)}{\partial x_0^2} + \frac{\partial F_3(\zeta(t))}{\partial y_0}\frac{\partial^2\Phi_3(t,\zeta_0)}{\partial x_0^2} + \frac{\partial F_3(\zeta(t))}{\partial y_1}\frac{\partial^2\Phi_4(t,\zeta_0)}{\partial x_0^2} \\
&+ \left(\frac{\partial^2 F_3(\zeta(t))}{\partial x_0^2}\frac{\partial\Phi_1(t,\zeta_0)}{\partial x_0} + \frac{\partial^2 F_3(\zeta(t))}{\partial x_0\partial x_1}\frac{\partial\Phi_2(t,\zeta_0)}{\partial x_0} + \frac{\partial^2 F_3(\zeta(t))}{\partial x_0\partial y_0}\frac{\partial\Phi_3(t,\zeta_0)}{\partial x_0} + \frac{\partial^2 F_3(\zeta(t))}{\partial x_0\partial y_1}\frac{\partial\Phi_4(t,\zeta_0)}{\partial x_0}\right)\frac{\partial\Phi_1(t,\zeta_0)}{\partial x_0} \\
&+ \left(\frac{\partial^2 F_3(\zeta(t))}{\partial x_0\partial x_1}\frac{\partial\Phi_1(t,\zeta_0)}{\partial x_0} + \frac{\partial^2 F_3(\zeta(t))}{\partial x_1^2}\frac{\partial\Phi_2(t,\zeta_0)}{\partial x_0} + \frac{\partial^2 F_3(\zeta(t))}{\partial x_1\partial y_0}\frac{\partial\Phi_3(t,\zeta_0)}{\partial x_0} + \frac{\partial^2 F_3(\zeta(t))}{\partial x_1\partial y_1}\frac{\partial\Phi_4(t,\zeta_0)}{\partial x_0}\right)\frac{\partial\Phi_2(t,\zeta_0)}{\partial x_0} \\
&+ \left(\frac{\partial^2 F_3(\zeta(t))}{\partial x_0\partial y_0}\frac{\partial\Phi_1(t,\zeta_0)}{\partial x_0} + \frac{\partial^2 F_3(\zeta(t))}{\partial x_1\partial y_0}\frac{\partial\Phi_2(t,\zeta_0)}{\partial x_0} + \frac{\partial^2 F_3(\zeta(t))}{\partial y_0^2}\frac{\partial\Phi_3(t,\zeta_0)}{\partial x_0} + \frac{\partial^2 F_3(\zeta(t))}{\partial y_0\partial y_1}\frac{\partial\Phi_4(t,\zeta_0)}{\partial x_0}\right)\frac{\partial\Phi_3(t,\zeta_0)}{\partial x_0} \\
&+ \left(\frac{\partial^2 F_3(\zeta(t))}{\partial x_0\partial y_1}\frac{\partial\Phi_1(t,\zeta_0)}{\partial x_0} + \frac{\partial^2 F_3(\zeta(t))}{\partial x_1\partial y_1}\frac{\partial\Phi_2(t,\zeta_0)}{\partial x_0} + \frac{\partial^2 F_3(\zeta(t))}{\partial y_0\partial y_1}\frac{\partial\Phi_3(t,\zeta_0)}{\partial x_0} + \frac{\partial^2 F_3(\zeta(t))}{\partial y_1^2}\frac{\partial\Phi_4(t,\zeta_0)}{\partial x_0}\right)\frac{\partial\Phi_4(t,\zeta_0)}{\partial x_0}
\end{aligned}$$

with the initial condition $\frac{\partial^2\Phi_3(0,\zeta_0)}{\partial x_0^2} = 0$, then

$$\frac{d}{dt}\left(\frac{\partial^2\Phi_3(t,\zeta_0)}{\partial x_0^2}\right) = \frac{\partial F_3(\zeta(t))}{\partial y_0}\frac{\partial^2\Phi_3(t,\zeta_0)}{\partial x_0^2} \tag{34}$$

with the initial condition $\frac{\partial^2\Phi_3(0,\zeta_0)}{\partial x_0^2} = 0$. From (34) we have

$$\frac{\partial^2\Phi_3(t,\zeta_0)}{\partial x_0^2} = 0.$$

$$\begin{aligned}
\frac{d}{dt}\left(\frac{\partial^2\Phi_3(t,\zeta_0)}{\partial x_0\partial x_1}\right) &= \frac{\partial F_3(\zeta(t))}{\partial x_0}\frac{\partial^2\Phi_1(t,\zeta_0)}{\partial x_0\partial x_1} + \frac{\partial F_3(\zeta(t))}{\partial x_1}\frac{\partial^2\Phi_2(t,\zeta_0)}{\partial x_0\partial x_1} + \frac{\partial F_3(\zeta(t))}{\partial y_0}\frac{\partial^2\Phi_3(t,\zeta_0)}{\partial x_0\partial x_1} + \frac{\partial F_3(\zeta(t))}{\partial y_1}\frac{\partial^2\Phi_4(t,\zeta_0)}{\partial x_0\partial x_1} \\
&+ \left(\frac{\partial^2 F_3(\zeta(t))}{\partial x_0^2}\frac{\partial\Phi_1(t,\zeta_0)}{\partial x_1} + \frac{\partial^2 F_3(\zeta(t))}{\partial x_0\partial x_1}\frac{\partial\Phi_2(t,\zeta_0)}{\partial x_1} + \frac{\partial^2 F_3(\zeta(t))}{\partial x_0\partial y_0}\frac{\partial\Phi_3(t,\zeta_0)}{\partial x_1} + \frac{\partial^2 F_3(\zeta(t))}{\partial x_0\partial y_1}\frac{\partial\Phi_4(t,\zeta_0)}{\partial x_1}\right)\frac{\partial\Phi_1(t,\zeta_0)}{\partial x_0} \\
&+ \left(\frac{\partial^2 F_3(\zeta(t))}{\partial x_0\partial x_1}\frac{\partial\Phi_1(t,\zeta_0)}{\partial x_1} + \frac{\partial^2 F_3(\zeta(t))}{\partial x_1^2}\frac{\partial\Phi_2(t,\zeta_0)}{\partial x_1} + \frac{\partial^2 F_3(\zeta(t))}{\partial x_1\partial y_0}\frac{\partial\Phi_3(t,\zeta_0)}{\partial x_1} + \frac{\partial^2 F_3(\zeta(t))}{\partial x_1\partial y_1}\frac{\partial\Phi_4(t,\zeta_0)}{\partial x_1}\right)\frac{\partial\Phi_2(t,\zeta_0)}{\partial x_0} \\
&+ \left(\frac{\partial^2 F_3(\zeta(t))}{\partial x_0\partial y_0}\frac{\partial\Phi_1(t,\zeta_0)}{\partial x_1} + \frac{\partial^2 F_3(\zeta(t))}{\partial x_1\partial y_0}\frac{\partial\Phi_2(t,\zeta_0)}{\partial x_1} + \frac{\partial^2 F_3(\zeta(t))}{\partial y_0^2}\frac{\partial\Phi_3(t,\zeta_0)}{\partial x_1} + \frac{\partial^2 F_3(\zeta(t))}{\partial y_0\partial y_1}\frac{\partial\Phi_4(t,\zeta_0)}{\partial x_1}\right)\frac{\partial\Phi_3(t,\zeta_0)}{\partial x_0} \\
&+ \left(\frac{\partial^2 F_3(\zeta(t))}{\partial x_0\partial y_1}\frac{\partial\Phi_1(t,\zeta_0)}{\partial x_1} + \frac{\partial^2 F_3(\zeta(t))}{\partial x_1\partial y_1}\frac{\partial\Phi_2(t,\zeta_0)}{\partial x_1} + \frac{\partial^2 F_3(\zeta(t))}{\partial y_0\partial y_1}\frac{\partial\Phi_3(t,\zeta_0)}{\partial x_1} + \frac{\partial^2 F_3(\zeta(t))}{\partial y_1^2}\frac{\partial\Phi_4(t,\zeta_0)}{\partial x_1}\right)\frac{\partial\Phi_4(t,\zeta_0)}{\partial x_0}
\end{aligned}$$

with the initial condition $\frac{\partial^2\Phi_3(0,\zeta_0)}{\partial x_0\partial x_1} = 0$, then

$$\frac{d}{dt}\left(\frac{\partial^2\Phi_3(t,\zeta_0)}{\partial x_0\partial x_1}\right) = \frac{\partial F_3(\zeta(t))}{\partial y_0}\frac{\partial^2\Phi_3(t,\zeta_0)}{\partial x_0\partial x_1} \tag{35}$$

with the initial condition $\frac{\partial^2\Phi_3(0,\zeta_0)}{\partial x_0\partial x_1} = 0$. From (35) we have

$$\frac{\partial^2\Phi_3(t,\zeta_0)}{\partial x_0\partial x_1} = 0.$$

$$\begin{aligned}
\frac{d}{dt}\left(\frac{\partial^2\Phi_3(t,\zeta_0)}{\partial x_0\partial y_0}\right) &= \frac{\partial F_3(\zeta(t))}{\partial x_0}\frac{\partial^2\Phi_1(t,\zeta_0)}{\partial x_0\partial y_0} + \frac{\partial F_3(\zeta(t))}{\partial x_1}\frac{\partial^2\Phi_2(t,\zeta_0)}{\partial x_0\partial y_0} + \frac{\partial F_3(\zeta(t))}{\partial y_0}\frac{\partial^2\Phi_3(t,\zeta_0)}{\partial x_0\partial y_0} + \frac{\partial F_3(\zeta(t))}{\partial y_1}\frac{\partial^2\Phi_4(t,\zeta_0)}{\partial x_0\partial y_0} \\
&+ \left(\frac{\partial^2 F_3(\zeta(t))}{\partial x_0^2}\frac{\partial\Phi_1(t,\zeta_0)}{\partial y_0} + \frac{\partial^2 F_3(\zeta(t))}{\partial x_0\partial x_1}\frac{\partial\Phi_2(t,\zeta_0)}{\partial y_0} + \frac{\partial^2 F_3(\zeta(t))}{\partial x_0\partial y_0}\frac{\partial\Phi_3(t,\zeta_0)}{\partial y_0} + \frac{\partial^2 F_3(\zeta(t))}{\partial x_0\partial y_1}\frac{\partial\Phi_4(t,\zeta_0)}{\partial y_0}\right)\frac{\partial\Phi_1(t,\zeta_0)}{\partial x_0} \\
&+ \left(\frac{\partial^2 F_3(\zeta(t))}{\partial x_0\partial x_1}\frac{\partial\Phi_1(t,\zeta_0)}{\partial y_0} + \frac{\partial^2 F_3(\zeta(t))}{\partial x_1^2}\frac{\partial\Phi_2(t,\zeta_0)}{\partial y_0} + \frac{\partial^2 F_3(\zeta(t))}{\partial x_1\partial y_0}\frac{\partial\Phi_3(t,\zeta_0)}{\partial y_0} + \frac{\partial^2 F_3(\zeta(t))}{\partial x_1\partial y_1}\frac{\partial\Phi_4(t,\zeta_0)}{\partial y_0}\right)\frac{\partial\Phi_2(t,\zeta_0)}{\partial x_0} \\
&+ \left(\frac{\partial^2 F_3(\zeta(t))}{\partial x_0\partial y_0}\frac{\partial\Phi_1(t,\zeta_0)}{\partial y_0} + \frac{\partial^2 F_3(\zeta(t))}{\partial x_1\partial y_0}\frac{\partial\Phi_2(t,\zeta_0)}{\partial y_0} + \frac{\partial^2 F_3(\zeta(t))}{\partial y_0^2}\frac{\partial\Phi_3(t,\zeta_0)}{\partial y_0} + \frac{\partial^2 F_3(\zeta(t))}{\partial y_0\partial y_1}\frac{\partial\Phi_4(t,\zeta_0)}{\partial y_0}\right)\frac{\partial\Phi_3(t,\zeta_0)}{\partial x_0} \\
&+ \left(\frac{\partial^2 F_3(\zeta(t))}{\partial x_0\partial y_1}\frac{\partial\Phi_1(t,\zeta_0)}{\partial y_0} + \frac{\partial^2 F_3(\zeta(t))}{\partial x_1\partial y_1}\frac{\partial\Phi_2(t,\zeta_0)}{\partial y_0} + \frac{\partial^2 F_3(\zeta(t))}{\partial y_0\partial y_1}\frac{\partial\Phi_3(t,\zeta_0)}{\partial y_0} + \frac{\partial^2 F_3(\zeta(t))}{\partial y_1^2}\frac{\partial\Phi_4(t,\zeta_0)}{\partial y_0}\right)\frac{\partial\Phi_4(t,\zeta_0)}{\partial x_0}
\end{aligned}$$

with the initial condition $\frac{\partial^2\Phi_3(0,\zeta_0)}{\partial x_0\partial y_0}=0$, then

$$\frac{d}{dt}\left(\frac{\partial^2\Phi_3(t,\zeta_0)}{\partial x_0\partial y_0}\right)=\frac{\partial F_3(\zeta(t))}{\partial y_0}\frac{\partial^2\Phi_3(t,\zeta_0)}{\partial x_0\partial y_0}+\frac{\partial^2 F_3(\zeta(t))}{\partial x_1\partial y_0}\frac{\partial\Phi_3(t,\zeta_0)}{\partial y_0}\frac{\partial\Phi_2(t,\zeta_0)}{\partial x_0} \tag{36}$$

with the initial condition $\frac{\partial^2\Phi_3(0,\zeta_0)}{\partial x_0\partial y_0}=0$. From (36) we have

$$\frac{\partial^2\Phi_3(t,\zeta_0)}{\partial x_0\partial y_0}=e^{\frac{\partial F_3(\zeta(t))}{\partial y_0}t}\int_0^t\frac{\partial^2 F_3(\zeta(s))}{\partial x_1\partial y_0}\frac{\partial\Phi_2(s,\zeta_0)}{\partial x_0}ds.$$

$$\begin{aligned}
\frac{d}{dt}\left(\frac{\partial^2\Phi_3(t,\zeta_0)}{\partial x_0\partial y_1}\right)&=\frac{\partial F_3(\zeta(t))}{\partial x_0}\frac{\partial^2\Phi_1(t,\zeta_0)}{\partial x_0\partial y_1}+\frac{\partial F_3(\zeta(t))}{\partial x_1}\frac{\partial^2\Phi_2(t,\zeta_0)}{\partial x_0\partial y_1}+\frac{\partial F_3(\zeta(t))}{\partial y_0}\frac{\partial^2\Phi_3(t,\zeta_0)}{\partial x_0\partial y_1}+\frac{\partial F_3(\zeta(t))}{\partial y_1}\frac{\partial^2\Phi_4(t,\zeta_0)}{\partial x_0\partial y_1}\\
&+\left(\frac{\partial^2 F_3(\zeta(t))}{\partial x_0^2}\frac{\partial\Phi_1(t,\zeta_0)}{\partial y_1}+\frac{\partial^2 F_3(\zeta(t))}{\partial x_0\partial x_1}\frac{\partial\Phi_2(t,\zeta_0)}{\partial y_1}+\frac{\partial^2 F_3(\zeta(t))}{\partial x_0\partial y_0}\frac{\partial\Phi_3(t,\zeta_0)}{\partial y_1}+\frac{\partial^2 F_3(\zeta(t))}{\partial x_0\partial y_1}\frac{\partial\Phi_4(t,\zeta_0)}{\partial y_1}\right)\frac{\partial\Phi_1(t,\zeta_0)}{\partial x_0}\\
&+\left(\frac{\partial^2 F_3(\zeta(t))}{\partial x_0\partial x_1}\frac{\partial\Phi_1(t,\zeta_0)}{\partial y_1}+\frac{\partial^2 F_3(\zeta(t))}{\partial x_1^2}\frac{\partial\Phi_2(t,\zeta_0)}{\partial y_1}+\frac{\partial^2 F_3(\zeta(t))}{\partial x_1\partial y_0}\frac{\partial\Phi_3(t,\zeta_0)}{\partial y_1}+\frac{\partial^2 F_3(\zeta(t))}{\partial x_1\partial y_1}\frac{\partial\Phi_4(t,\zeta_0)}{\partial y_1}\right)\frac{\partial\Phi_2(t,\zeta_0)}{\partial x_0}\\
&+\left(\frac{\partial^2 F_3(\zeta(t))}{\partial x_0\partial y_0}\frac{\partial\Phi_1(t,\zeta_0)}{\partial y_1}+\frac{\partial^2 F_3(\zeta(t))}{\partial x_1\partial y_0}\frac{\partial\Phi_2(t,\zeta_0)}{\partial y_1}+\frac{\partial^2 F_3(\zeta(t))}{\partial y_0^2}\frac{\partial\Phi_3(t,\zeta_0)}{\partial y_1}+\frac{\partial^2 F_3(\zeta(t))}{\partial y_0\partial y_1}\frac{\partial\Phi_4(t,\zeta_0)}{\partial y_1}\right)\frac{\partial\Phi_3(t,\zeta_0)}{\partial x_0}\\
&+\left(\frac{\partial^2 F_3(\zeta(t))}{\partial x_0\partial y_1}\frac{\partial\Phi_1(t,\zeta_0)}{\partial y_1}+\frac{\partial^2 F_3(\zeta(t))}{\partial x_1\partial y_1}\frac{\partial\Phi_2(t,\zeta_0)}{\partial y_1}+\frac{\partial^2 F_3(\zeta(t))}{\partial y_0\partial y_1}\frac{\partial\Phi_3(t,\zeta_0)}{\partial y_1}+\frac{\partial^2 F_3(\zeta(t))}{\partial y_1^2}\frac{\partial\Phi_4(t,\zeta_0)}{\partial y_1}\right)\frac{\partial\Phi_4(t,\zeta_0)}{\partial x_0}
\end{aligned}$$

with the initial condition $\frac{\partial^2\Phi_3(0,\zeta_0)}{\partial x_0\partial y_1}=0$, then

$$\frac{d}{dt}\left(\frac{\partial^2\Phi_3(t,\zeta_0)}{\partial x_0\partial y_1}\right)=\frac{\partial F_3(\zeta(t))}{\partial y_0}\frac{\partial^2\Phi_3(t,\zeta_0)}{\partial x_0\partial y_1} \tag{37}$$

with the initial condition $\frac{\partial^2\Phi_3(0,\zeta_0)}{\partial x_0\partial y_1}=0$. From (37) we have

$$\frac{\partial^2\Phi_3(t,\zeta_0)}{\partial x_0\partial y_1}=0.$$

$$\begin{aligned}
\frac{d}{dt}\left(\frac{\partial^2\Phi_3(t,\zeta_0)}{\partial x_1^2}\right)&=\frac{\partial F_3(\zeta(t))}{\partial x_0}\frac{\partial^2\Phi_1(t,\zeta_0)}{\partial x_1^2}+\frac{\partial F_3(\zeta(t))}{\partial x_1}\frac{\partial^2\Phi_2(t,\zeta_0)}{\partial x_1^2}+\frac{\partial F_3(\zeta(t))}{\partial y_0}\frac{\partial^2\Phi_3(t,\zeta_0)}{\partial x_1^2}+\frac{\partial F_3(\zeta(t))}{\partial y_1}\frac{\partial^2\Phi_4(t,\zeta_0)}{\partial x_1^2}\\
&+\left(\frac{\partial^2 F_3(\zeta(t))}{\partial x_0^2}\frac{\partial\Phi_1(t,\zeta_0)}{\partial x_1}+\frac{\partial^2 F_3(\zeta(t))}{\partial x_0\partial x_1}\frac{\partial\Phi_2(t,\zeta_0)}{\partial x_1}+\frac{\partial^2 F_3(\zeta(t))}{\partial x_0\partial y_0}\frac{\partial\Phi_3(t,\zeta_0)}{\partial x_1}+\frac{\partial^2 F_3(\zeta(t))}{\partial x_0\partial y_1}\frac{\partial\Phi_4(t,\zeta_0)}{\partial x_1}\right)\frac{\partial\Phi_1(t,\zeta_0)}{\partial x_1}\\
&+\left(\frac{\partial^2 F_3(\zeta(t))}{\partial x_0\partial x_1}\frac{\partial\Phi_1(t,\zeta_0)}{\partial x_1}+\frac{\partial^2 F_3(\zeta(t))}{\partial x_1^2}\frac{\partial\Phi_2(t,\zeta_0)}{\partial x_1}+\frac{\partial^2 F_3(\zeta(t))}{\partial x_1\partial y_0}\frac{\partial\Phi_3(t,\zeta_0)}{\partial x_1}+\frac{\partial^2 F_3(\zeta(t))}{\partial x_1\partial y_1}\frac{\partial\Phi_4(t,\zeta_0)}{\partial x_1}\right)\frac{\partial\Phi_2(t,\zeta_0)}{\partial x_1}\\
&+\left(\frac{\partial^2 F_3(\zeta(t))}{\partial x_0\partial y_0}\frac{\partial\Phi_1(t,\zeta_0)}{\partial x_1}+\frac{\partial^2 F_3(\zeta(t))}{\partial x_1\partial y_0}\frac{\partial\Phi_2(t,\zeta_0)}{\partial x_1}+\frac{\partial^2 F_3(\zeta(t))}{\partial y_0^2}\frac{\partial\Phi_3(t,\zeta_0)}{\partial x_1}+\frac{\partial^2 F_3(\zeta(t))}{\partial y_0\partial y_1}\frac{\partial\Phi_4(t,\zeta_0)}{\partial x_1}\right)\frac{\partial\Phi_3(t,\zeta_0)}{\partial x_1}\\
&+\left(\frac{\partial^2 F_3(\zeta(t))}{\partial x_0\partial y_1}\frac{\partial\Phi_1(t,\zeta_0)}{\partial x_1}+\frac{\partial^2 F_3(\zeta(t))}{\partial x_1\partial y_1}\frac{\partial\Phi_2(t,\zeta_0)}{\partial x_1}+\frac{\partial^2 F_3(\zeta(t))}{\partial y_0\partial y_1}\frac{\partial\Phi_3(t,\zeta_0)}{\partial x_1}+\frac{\partial^2 F_3(\zeta(t))}{\partial y_1^2}\frac{\partial\Phi_4(t,\zeta_0)}{\partial x_1}\right)\frac{\partial\Phi_4(t,\zeta_0)}{\partial x_1}
\end{aligned}$$

with the initial condition $\frac{\partial^2\Phi_3(0,\zeta_0)}{\partial x_1^2}=0$, then

$$\frac{d}{dt}\left(\frac{\partial^2\Phi_3(t,\zeta_0)}{\partial x_1^2}\right)=\frac{\partial F_3(\zeta(t))}{\partial y_0}\frac{\partial^2\Phi_3(t,\zeta_0)}{\partial x_1^2} \tag{38}$$

with the initial condition $\frac{\partial^2\Phi_3(0,\zeta_0)}{\partial x_1^2}=0$. From (38) we have

$$\frac{\partial^2\Phi_3(t,\zeta_0)}{\partial x_1^2}=0.$$

$$\begin{aligned}
\frac{d}{dt}\left(\frac{\partial^2\Phi_3(t,\zeta_0)}{\partial x_1\partial y_0}\right)&=\frac{\partial F_3(\zeta(t))}{\partial x_0}\frac{\partial^2\Phi_1(t,\zeta_0)}{\partial x_1\partial y_0}+\frac{\partial F_3(\zeta(t))}{\partial x_1}\frac{\partial^2\Phi_2(t,\zeta_0)}{\partial x_1\partial y_0}+\frac{\partial F_3(\zeta(t))}{\partial y_0}\frac{\partial^2\Phi_3(t,\zeta_0)}{\partial x_1\partial y_0}+\frac{\partial F_3(\zeta(t))}{\partial y_1}\frac{\partial^2\Phi_4(t,\zeta_0)}{\partial x_1\partial y_0}\\
&+\left(\frac{\partial^2 F_3(\zeta(t))}{\partial x_0^2}\frac{\partial\Phi_1(t,\zeta_0)}{\partial y_0}+\frac{\partial^2 F_3(\zeta(t))}{\partial x_0\partial x_1}\frac{\partial\Phi_2(t,\zeta_0)}{\partial y_0}+\frac{\partial^2 F_3(\zeta(t))}{\partial x_0\partial y_0}\frac{\partial\Phi_3(t,\zeta_0)}{\partial y_0}+\frac{\partial^2 F_3(\zeta(t))}{\partial x_0\partial y_1}\frac{\partial\Phi_4(t,\zeta_0)}{\partial y_0}\right)\frac{\partial\Phi_1(t,\zeta_0)}{\partial x_1}\\
&+\left(\frac{\partial^2 F_3(\zeta(t))}{\partial x_0\partial x_1}\frac{\partial\Phi_1(t,\zeta_0)}{\partial y_0}+\frac{\partial^2 F_3(\zeta(t))}{\partial x_1^2}\frac{\partial\Phi_2(t,\zeta_0)}{\partial y_0}+\frac{\partial^2 F_3(\zeta(t))}{\partial x_1\partial y_0}\frac{\partial\Phi_3(t,\zeta_0)}{\partial y_0}+\frac{\partial^2 F_3(\zeta(t))}{\partial x_1\partial y_1}\frac{\partial\Phi_4(t,\zeta_0)}{\partial y_0}\right)\frac{\partial\Phi_2(t,\zeta_0)}{\partial x_1}\\
&+\left(\frac{\partial^2 F_3(\zeta(t))}{\partial x_0\partial y_0}\frac{\partial\Phi_1(t,\zeta_0)}{\partial y_0}+\frac{\partial^2 F_3(\zeta(t))}{\partial x_1\partial y_0}\frac{\partial\Phi_2(t,\zeta_0)}{\partial y_0}+\frac{\partial^2 F_3(\zeta(t))}{\partial y_0^2}\frac{\partial\Phi_3(t,\zeta_0)}{\partial y_0}+\frac{\partial^2 F_3(\zeta(t))}{\partial y_0\partial y_1}\frac{\partial\Phi_4(t,\zeta_0)}{\partial y_0}\right)\frac{\partial\Phi_3(t,\zeta_0)}{\partial x_1}\\
&+\left(\frac{\partial^2 F_3(\zeta(t))}{\partial x_0\partial y_1}\frac{\partial\Phi_1(t,\zeta_0)}{\partial y_0}+\frac{\partial^2 F_3(\zeta(t))}{\partial x_1\partial y_1}\frac{\partial\Phi_2(t,\zeta_0)}{\partial y_0}+\frac{\partial^2 F_3(\zeta(t))}{\partial y_0\partial y_1}\frac{\partial\Phi_3(t,\zeta_0)}{\partial y_0}+\frac{\partial^2 F_3(\zeta(t))}{\partial y_1^2}\frac{\partial\Phi_4(t,\zeta_0)}{\partial y_0}\right)\frac{\partial\Phi_4(t,\zeta_0)}{\partial x_1}
\end{aligned}$$

with the initial condition $\frac{\partial^2\Phi_3(0,\zeta_0)}{\partial x_1\partial y_0}=0$, then

$$\frac{d}{dt}\left(\frac{\partial^2\Phi_3(t,\zeta_0)}{\partial x_1\partial y_0}\right)=\frac{\partial F_3(\zeta(t))}{\partial y_0}\frac{\partial^2\Phi_3(t,\zeta_0)}{\partial x_1\partial y_0}+\frac{\partial^2 F_3(\zeta(t))}{\partial x_1\partial y_0}\frac{\partial\Phi_3(t,\zeta_0)}{\partial y_0}\frac{\partial\Phi_2(t,\zeta_0)}{\partial x_1} \tag{39}$$

with the initial condition $\frac{\partial^2\Phi_3(0,\zeta_0)}{\partial x_1\partial y_0}=0$. From (39) we have

$$\frac{\partial^2\Phi_3(t,\zeta_0)}{\partial x_1\partial y_0}=e^{\frac{\partial F_3(\zeta(t))}{\partial y_0}t}\int_0^t\frac{\partial^2 F_3(\zeta(s))}{\partial x_1\partial y_0}\frac{\partial\Phi_2(s,\zeta_0)}{\partial x_1}ds.$$

$$\begin{aligned}\frac{d}{dt}\left(\frac{\partial^2\Phi_3(t,\zeta_0)}{\partial x_1\partial y_1}\right)&=\frac{\partial F_3(\zeta(t))}{\partial x_0}\frac{\partial^2\Phi_1(t,\zeta_0)}{\partial x_1\partial y_1}+\frac{\partial F_3(\zeta(t))}{\partial x_1}\frac{\partial^2\Phi_2(t,\zeta_0)}{\partial x_1\partial y_1}+\frac{\partial F_3(\zeta(t))}{\partial y_0}\frac{\partial^2\Phi_3(t,\zeta_0)}{\partial x_1\partial y_1}+\frac{\partial F_3(\zeta(t))}{\partial y_1}\frac{\partial^2\Phi_4(t,\zeta_0)}{\partial x_1\partial y_1}\\
&+\left(\frac{\partial^2 F_3(\zeta(t))}{\partial x_0^2}\frac{\partial\Phi_1(t,\zeta_0)}{\partial y_1}+\frac{\partial^2 F_3(\zeta(t))}{\partial x_0\partial x_1}\frac{\partial\Phi_2(t,\zeta_0)}{\partial y_1}+\frac{\partial^2 F_3(\zeta(t))}{\partial x_0\partial y_0}\frac{\partial\Phi_3(t,\zeta_0)}{\partial y_1}+\frac{\partial^2 F_3(\zeta(t))}{\partial x_0\partial y_1}\frac{\partial\Phi_4(t,\zeta_0)}{\partial y_1}\right)\frac{\partial\Phi_1(t,\zeta_0)}{\partial x_1}\\
&+\left(\frac{\partial^2 F_3(\zeta(t))}{\partial x_0\partial x_1}\frac{\partial\Phi_1(t,\zeta_0)}{\partial y_1}+\frac{\partial^2 F_3(\zeta(t))}{\partial x_1^2}\frac{\partial\Phi_2(t,\zeta_0)}{\partial y_1}+\frac{\partial^2 F_3(\zeta(t))}{\partial x_1\partial y_0}\frac{\partial\Phi_3(t,\zeta_0)}{\partial y_1}+\frac{\partial^2 F_3(\zeta(t))}{\partial x_1\partial y_1}\frac{\partial\Phi_4(t,\zeta_0)}{\partial y_1}\right)\frac{\partial\Phi_2(t,\zeta_0)}{\partial x_1}\\
&+\left(\frac{\partial^2 F_3(\zeta(t))}{\partial x_0\partial y_0}\frac{\partial\Phi_1(t,\zeta_0)}{\partial y_1}+\frac{\partial^2 F_3(\zeta(t))}{\partial x_1\partial y_0}\frac{\partial\Phi_2(t,\zeta_0)}{\partial y_1}+\frac{\partial^2 F_3(\zeta(t))}{\partial y_0^2}\frac{\partial\Phi_3(t,\zeta_0)}{\partial y_1}+\frac{\partial^2 F_3(\zeta(t))}{\partial y_0\partial y_1}\frac{\partial\Phi_4(t,\zeta_0)}{\partial y_1}\right)\frac{\partial\Phi_3(t,\zeta_0)}{\partial x_1}\\
&+\left(\frac{\partial^2 F_3(\zeta(t))}{\partial x_0\partial y_1}\frac{\partial\Phi_1(t,\zeta_0)}{\partial y_1}+\frac{\partial^2 F_3(\zeta(t))}{\partial x_1\partial y_1}\frac{\partial\Phi_2(t,\zeta_0)}{\partial y_1}+\frac{\partial^2 F_3(\zeta(t))}{\partial y_0\partial y_1}\frac{\partial\Phi_3(t,\zeta_0)}{\partial y_1}+\frac{\partial^2 F_3(\zeta(t))}{\partial y_1^2}\frac{\partial\Phi_4(t,\zeta_0)}{\partial y_1}\right)\frac{\partial\Phi_4(t,\zeta_0)}{\partial x_1}\end{aligned}$$

with the initial condition $\frac{\partial^2\Phi_3(0,\zeta_0)}{\partial x_1\partial y_1}=0$, then

$$\frac{d}{dt}\left(\frac{\partial^2\Phi_3(t,\zeta_0)}{\partial x_1\partial y_1}\right)=\frac{\partial F_3(\zeta(t))}{\partial y_0}\frac{\partial^2\Phi_3(t,\zeta_0)}{\partial x_1\partial y_1} \tag{40}$$

with the initial condition $\frac{\partial^2\Phi_3(0,\zeta_0)}{\partial x_1\partial y_1}=0$. From (40) we have

$$\frac{\partial^2\Phi_3(t,\zeta_0)}{\partial x_1\partial y_1}=0.$$

$$\begin{aligned}\frac{d}{dt}\left(\frac{\partial^2\Phi_3(t,\zeta_0)}{\partial y_0^2}\right)&=\frac{\partial F_3(\zeta(t))}{\partial x_0}\frac{\partial^2\Phi_1(t,\zeta_0)}{\partial y_0^2}+\frac{\partial F_3(\zeta(t))}{\partial x_1}\frac{\partial^2\Phi_2(t,\zeta_0)}{\partial y_0^2}+\frac{\partial F_3(\zeta(t))}{\partial y_0}\frac{\partial^2\Phi_3(t,\zeta_0)}{\partial y_0^2}+\frac{\partial F_3(\zeta(t))}{\partial y_1}\frac{\partial^2\Phi_4(t,\zeta_0)}{\partial y_0^2}\\
&+\left(\frac{\partial^2 F_3(\zeta(t))}{\partial x_0^2}\frac{\partial\Phi_1(t,\zeta_0)}{\partial y_0}+\frac{\partial^2 F_3(\zeta(t))}{\partial x_0\partial x_1}\frac{\partial\Phi_2(t,\zeta_0)}{\partial y_0}+\frac{\partial^2 F_3(\zeta(t))}{\partial x_0\partial y_0}\frac{\partial\Phi_3(t,\zeta_0)}{\partial y_0}+\frac{\partial^2 F_3(\zeta(t))}{\partial x_0\partial y_1}\frac{\partial\Phi_4(t,\zeta_0)}{\partial y_0}\right)\frac{\partial\Phi_1(t,\zeta_0)}{\partial y_0}\\
&+\left(\frac{\partial^2 F_3(\zeta(t))}{\partial x_0\partial x_1}\frac{\partial\Phi_1(t,\zeta_0)}{\partial y_0}+\frac{\partial^2 F_3(\zeta(t))}{\partial x_1^2}\frac{\partial\Phi_2(t,\zeta_0)}{\partial y_0}+\frac{\partial^2 F_3(\zeta(t))}{\partial x_1\partial y_0}\frac{\partial\Phi_3(t,\zeta_0)}{\partial y_0}+\frac{\partial^2 F_3(\zeta(t))}{\partial x_1\partial y_1}\frac{\partial\Phi_4(t,\zeta_0)}{\partial y_0}\right)\frac{\partial\Phi_2(t,\zeta_0)}{\partial y_0}\\
&+\left(\frac{\partial^2 F_3(\zeta(t))}{\partial x_0\partial y_0}\frac{\partial\Phi_1(t,\zeta_0)}{\partial y_0}+\frac{\partial^2 F_3(\zeta(t))}{\partial x_1\partial y_0}\frac{\partial\Phi_2(t,\zeta_0)}{\partial y_0}+\frac{\partial^2 F_3(\zeta(t))}{\partial y_0^2}\frac{\partial\Phi_3(t,\zeta_0)}{\partial y_0}+\frac{\partial^2 F_3(\zeta(t))}{\partial y_0\partial y_1}\frac{\partial\Phi_4(t,\zeta_0)}{\partial y_0}\right)\frac{\partial\Phi_3(t,\zeta_0)}{\partial y_0}\\
&+\left(\frac{\partial^2 F_3(\zeta(t))}{\partial x_0\partial y_1}\frac{\partial\Phi_1(t,\zeta_0)}{\partial y_0}+\frac{\partial^2 F_3(\zeta(t))}{\partial x_1\partial y_1}\frac{\partial\Phi_2(t,\zeta_0)}{\partial y_0}+\frac{\partial^2 F_3(\zeta(t))}{\partial y_0\partial y_1}\frac{\partial\Phi_3(t,\zeta_0)}{\partial y_0}+\frac{\partial^2 F_3(\zeta(t))}{\partial y_1^2}\frac{\partial\Phi_4(t,\zeta_0)}{\partial y_0}\right)\frac{\partial\Phi_4(t,\zeta_0)}{\partial y_0}\end{aligned}$$

with the initial condition $\frac{\partial^2\Phi_3(0,\zeta_0)}{\partial y_0^2}=0$, then

$$\frac{d}{dt}\left(\frac{\partial^2\Phi_3(t,\zeta_0)}{\partial y_0^2}\right)=\frac{\partial F_3(\zeta(t))}{\partial y_0}\frac{\partial^2\Phi_3(t,\zeta_0)}{\partial y_0^2}+\left(\frac{\partial^2 F_3(\zeta(t))}{\partial y_0^2}\frac{\partial\Phi_3(t,\zeta_0)}{\partial y_0}+\frac{\partial^2 F_3(\zeta(t))}{\partial y_0\partial y_1}\frac{\partial\Phi_4(t,\zeta_0)}{\partial y_0}\right)\frac{\partial\Phi_3(t,\zeta_0)}{\partial y_0} \tag{41}$$

with the initial condition $\frac{\partial^2\Phi_3(0,\zeta_0)}{\partial y_0^2}=0$. From (41) we have

$$\frac{\partial^2\Phi_3(t,\zeta_0)}{\partial y_0^2}=e^{\frac{\partial F_3(\zeta(t))}{\partial y_0}t}\int_0^t\left(\frac{\partial^2 F_3(\zeta(s))}{\partial y_0^2}\frac{\partial\Phi_3(s,\zeta_0)}{\partial y_0}+\frac{\partial^2 F_3(\zeta(s))}{\partial y_0\partial y_1}\frac{\partial\Phi_4(s,\zeta_0)}{\partial y_0}\right)ds.$$

$$\begin{aligned}\frac{d}{dt}\left(\frac{\partial^2\Phi_3(t,\zeta_0)}{\partial y_0\partial y_1}\right)&=\frac{\partial F_3(\zeta(t))}{\partial x_0}\frac{\partial^2\Phi_1(t,\zeta_0)}{\partial y_0\partial y_1}+\frac{\partial F_3(\zeta(t))}{\partial x_1}\frac{\partial^2\Phi_2(t,\zeta_0)}{\partial y_0\partial y_1}+\frac{\partial F_3(\zeta(t))}{\partial y_0}\frac{\partial^2\Phi_3(t,\zeta_0)}{\partial y_0\partial y_1}+\frac{\partial F_3(\zeta(t))}{\partial y_1}\frac{\partial^2\Phi_4(t,\zeta_0)}{\partial y_0\partial y_1}\\
&+\left(\frac{\partial^2 F_3(\zeta(t))}{\partial x_0^2}\frac{\partial\Phi_1(t,\zeta_0)}{\partial y_1}+\frac{\partial^2 F_3(\zeta(t))}{\partial x_0\partial x_1}\frac{\partial\Phi_2(t,\zeta_0)}{\partial y_1}+\frac{\partial^2 F_3(\zeta(t))}{\partial x_0\partial y_0}\frac{\partial\Phi_3(t,\zeta_0)}{\partial y_1}+\frac{\partial^2 F_3(\zeta(t))}{\partial x_0\partial y_1}\frac{\partial\Phi_4(t,\zeta_0)}{\partial y_1}\right)\frac{\partial\Phi_1(t,\zeta_0)}{\partial y_0}\\
&+\left(\frac{\partial^2 F_3(\zeta(t))}{\partial x_0\partial x_1}\frac{\partial\Phi_1(t,\zeta_0)}{\partial y_1}+\frac{\partial^2 F_3(\zeta(t))}{\partial x_1^2}\frac{\partial\Phi_2(t,\zeta_0)}{\partial y_1}+\frac{\partial^2 F_3(\zeta(t))}{\partial x_1\partial y_0}\frac{\partial\Phi_3(t,\zeta_0)}{\partial y_1}+\frac{\partial^2 F_3(\zeta(t))}{\partial x_1\partial y_1}\frac{\partial\Phi_4(t,\zeta_0)}{\partial y_1}\right)\frac{\partial\Phi_2(t,\zeta_0)}{\partial y_0}\\
&+\left(\frac{\partial^2 F_3(\zeta(t))}{\partial x_0\partial y_0}\frac{\partial\Phi_1(t,\zeta_0)}{\partial y_1}+\frac{\partial^2 F_3(\zeta(t))}{\partial x_1\partial y_0}\frac{\partial\Phi_2(t,\zeta_0)}{\partial y_1}+\frac{\partial^2 F_3(\zeta(t))}{\partial y_0^2}\frac{\partial\Phi_3(t,\zeta_0)}{\partial y_1}+\frac{\partial^2 F_3(\zeta(t))}{\partial y_0\partial y_1}\frac{\partial\Phi_4(t,\zeta_0)}{\partial y_1}\right)\frac{\partial\Phi_3(t,\zeta_0)}{\partial y_0}\\
&+\left(\frac{\partial^2 F_3(\zeta(t))}{\partial x_0\partial y_1}\frac{\partial\Phi_1(t,\zeta_0)}{\partial y_1}+\frac{\partial^2 F_3(\zeta(t))}{\partial x_1\partial y_1}\frac{\partial\Phi_2(t,\zeta_0)}{\partial y_1}+\frac{\partial^2 F_3(\zeta(t))}{\partial y_0\partial y_1}\frac{\partial\Phi_3(t,\zeta_0)}{\partial y_1}+\frac{\partial^2 F_3(\zeta(t))}{\partial y_1^2}\frac{\partial\Phi_4(t,\zeta_0)}{\partial y_1}\right)\frac{\partial\Phi_4(t,\zeta_0)}{\partial y_0}\end{aligned}$$

with the initial condition $\frac{\partial^2\Phi_3(0,\zeta_0)}{\partial y_0\partial y_1}=0$, then

$$\frac{d}{dt}\left(\frac{\partial^2\Phi_3(t,\zeta_0)}{\partial y_0\partial y_1}\right)=\frac{\partial F_3(\zeta(t))}{\partial y_0}\frac{\partial^2\Phi_3(t,\zeta_0)}{\partial y_0\partial y_1}+\frac{\partial^2 F_3(\zeta(t))}{\partial y_0\partial y_1}\frac{\partial\Phi_4(t,\zeta_0)}{\partial y_1}\frac{\partial\Phi_3(t,\zeta_0)}{\partial y_0} \tag{42}$$

with the initial condition $\frac{\partial^2\Phi_3(0,\zeta_0)}{\partial y_0\partial y_1}=0$. From (42) we have

$$\frac{\partial^2\Phi_3(t,\zeta_0)}{\partial y_0\partial y_1}=e^{\frac{\partial F_3(\zeta(t))}{\partial y_0}t}\int_0^t\frac{\partial^2 F_3(\zeta(s))}{\partial y_0\partial y_1}\frac{\partial\Phi_4(s,\zeta_0)}{\partial y_1}ds.$$

$$\begin{aligned}\frac{d}{dt}\left(\frac{\partial^2\Phi_3(t,\zeta_0)}{\partial y_1^2}\right)&=\frac{\partial F_3(\zeta(t))}{\partial x_0}\frac{\partial^2\Phi_1(t,\zeta_0)}{\partial y_1^2}+\frac{\partial F_3(\zeta(t))}{\partial x_1}\frac{\partial^2\Phi_2(t,\zeta_0)}{\partial y_1^2}+\frac{\partial F_3(\zeta(t))}{\partial y_0}\frac{\partial^2\Phi_3(t,\zeta_0)}{\partial y_1^2}+\frac{\partial F_3(\zeta(t))}{\partial y_1}\frac{\partial^2\Phi_4(t,\zeta_0)}{\partial y_1^2}\\
&+\left(\frac{\partial^2 F_3(\zeta(t))}{\partial x_0^2}\frac{\partial\Phi_1(t,\zeta_0)}{\partial y_1}+\frac{\partial^2 F_3(\zeta(t))}{\partial x_0\partial x_1}\frac{\partial\Phi_2(t,\zeta_0)}{\partial y_1}+\frac{\partial^2 F_3(\zeta(t))}{\partial x_0\partial y_0}\frac{\partial\Phi_3(t,\zeta_0)}{\partial y_1}+\frac{\partial^2 F_3(\zeta(t))}{\partial x_0\partial y_1}\frac{\partial\Phi_4(t,\zeta_0)}{\partial y_1}\right)\frac{\partial\Phi_1(t,\zeta_0)}{\partial y_1}\\
&+\left(\frac{\partial^2 F_3(\zeta(t))}{\partial x_0\partial x_1}\frac{\partial\Phi_1(t,\zeta_0)}{\partial y_1}+\frac{\partial^2 F_3(\zeta(t))}{\partial x_1^2}\frac{\partial\Phi_2(t,\zeta_0)}{\partial y_1}+\frac{\partial^2 F_3(\zeta(t))}{\partial x_1\partial y_0}\frac{\partial\Phi_3(t,\zeta_0)}{\partial y_1}+\frac{\partial^2 F_3(\zeta(t))}{\partial x_1\partial y_1}\frac{\partial\Phi_4(t,\zeta_0)}{\partial y_1}\right)\frac{\partial\Phi_2(t,\zeta_0)}{\partial y_1}\\
&+\left(\frac{\partial^2 F_3(\zeta(t))}{\partial x_0\partial y_0}\frac{\partial\Phi_1(t,\zeta_0)}{\partial y_1}+\frac{\partial^2 F_3(\zeta(t))}{\partial x_1\partial y_0}\frac{\partial\Phi_2(t,\zeta_0)}{\partial y_1}+\frac{\partial^2 F_3(\zeta(t))}{\partial y_0^2}\frac{\partial\Phi_3(t,\zeta_0)}{\partial y_1}+\frac{\partial^2 F_3(\zeta(t))}{\partial y_0\partial y_1}\frac{\partial\Phi_4(t,\zeta_0)}{\partial y_1}\right)\frac{\partial\Phi_3(t,\zeta_0)}{\partial y_1}\\
&+\left(\frac{\partial^2 F_3(\zeta(t))}{\partial x_0\partial y_1}\frac{\partial\Phi_1(t,\zeta_0)}{\partial y_1}+\frac{\partial^2 F_3(\zeta(t))}{\partial x_1\partial y_1}\frac{\partial\Phi_2(t,\zeta_0)}{\partial y_1}+\frac{\partial^2 F_3(\zeta(t))}{\partial y_0\partial y_1}\frac{\partial\Phi_3(t,\zeta_0)}{\partial y_1}+\frac{\partial^2 F_3(\zeta(t))}{\partial y_1^2}\frac{\partial\Phi_4(t,\zeta_0)}{\partial y_1}\right)\frac{\partial\Phi_4(t,\zeta_0)}{\partial y_1}\end{aligned}$$

with the initial condition $\frac{\partial^2\Phi_3(0,\zeta_0)}{\partial y_1^2}=0$, then

$$\frac{d}{dt}\left(\frac{\partial^2\Phi_3(t,\zeta_0)}{\partial y_1^2}\right)=\frac{\partial F_3(\zeta(t))}{\partial y_0}\frac{\partial^2\Phi_3(t,\zeta_0)}{\partial y_1^2} \tag{43}$$

with the initial condition $\frac{\partial^2\Phi_3(0,\zeta_0)}{\partial y_1^2}=0$. From (43) we have

$$\frac{\partial^2\Phi_3(t,\zeta_0)}{\partial y_1^2}=0.$$

4.3. First derivatives of Z^*

Let $\eta(\bar\tau)=\tau_0+\bar\tau$, $\eta_1(\bar\tau,\sigma)=x_0^*+q_1\sigma+z_1^*(\bar\tau,\sigma)$, $\eta_2(\bar\tau,\sigma)=\frac{a_x}{d_1}x_0^*+q_2\sigma+z_2^*(\bar\tau,\sigma)$, $\eta_3(\bar\tau,\sigma)=\sigma$ and $\eta_4(\bar\tau,\sigma)=q_4\sigma+z_4^*(\bar\tau,\sigma)$.
From (23) we have

$$\begin{cases}\frac{\partial}{\partial\bar\tau}(\eta_1-\Theta_1\circ\Phi(\eta,\eta_1,\eta_2,\eta_3,\eta_4))(0,0)=0,\\ \frac{\partial}{\partial\bar\tau}(\eta_2-\Theta_2\circ\Phi(\eta,\eta_1,\eta_2,\eta_3,\eta_4))(0,0)=0,\\ \frac{\partial}{\partial\bar\tau}(\eta_4-\Theta_4\circ\Phi(\eta,\eta_1,\eta_2,\eta_3,\eta_4))(0,0)=0.\end{cases}$$

Therefore

$$\begin{cases}\frac{\partial z_1^*(0,0)}{\partial\bar\tau}-\frac{\partial\Theta_1(\Phi(\tau_0,\zeta_0))}{\partial x_0}\left(\frac{\partial\Phi_1(\tau_0,\zeta_0)}{\partial\bar\tau}+\frac{\partial\Phi_1(\tau_0,\zeta_0)}{\partial x_0}\frac{\partial z_1^*(0,0)}{\partial\bar\tau}+\frac{\partial\Phi_1(\tau_0,\zeta_0)}{\partial x_1}\frac{\partial z_2^*(0,0)}{\partial\bar\tau}\right.\\ \qquad\left.+\frac{\partial\Phi_1(\tau_0,\zeta_0)}{\partial y_1}\frac{\partial z_4^*(0,0)}{\partial\bar\tau}\right)=0,\\ \frac{\partial z_2^*(0,0)}{\partial\bar\tau}-\frac{\partial\Theta_2(\Phi(\tau_0,\zeta_0))}{\partial x_1}\left(\frac{\partial\Phi_2(\tau_0,\zeta_0)}{\partial\bar\tau}+\frac{\partial\Phi_2(\tau_0,\zeta_0)}{\partial x_0}\frac{\partial z_1^*(0,0)}{\partial\bar\tau}+\frac{\partial\Phi_2(\tau_0,\zeta_0)}{\partial x_1}\frac{\partial z_2^*(0,0)}{\partial\bar\tau}\right.\\ \qquad\left.+\frac{\partial\Phi_2(\tau_0,\zeta_0)}{\partial y_1}\frac{\partial z_4^*(0,0)}{\partial\bar\tau}\right)=0,\\ \frac{\partial z_4^*(0,0)}{\partial\bar\tau}-\frac{\partial\Theta_4(\Phi(\tau_0,\zeta_0))}{\partial y_1}\left(\frac{\partial\Phi_4(\tau_0,\zeta_0)}{\partial\bar\tau}+\frac{\partial\Phi_4(\tau_0,\zeta_0)}{\partial x_0}\frac{\partial z_1^*(0,0)}{\partial\bar\tau}+\frac{\partial\Phi_4(\tau_0,\zeta_0)}{\partial x_1}\frac{\partial z_2^*(0,0)}{\partial\bar\tau}\right.\\ \qquad\left.+\frac{\partial\Phi_4(\tau_0,\zeta_0)}{\partial y_1}\frac{\partial z_4^*(0,0)}{\partial\bar\tau}\right)=0.\end{cases}$$

Since $\frac{\partial \Phi_1(\tau_0,\zeta_0)}{\partial \bar{\tau}} = \frac{\partial \Phi_2(\tau_0,\zeta_0)}{\partial \bar{\tau}} = \frac{\partial \Phi_4(\tau_0,\zeta_0)}{\partial \bar{\tau}} = 0$, we obtain

$$\begin{cases} a_0 \frac{\partial z_1^*(0,0)}{\partial \bar{\tau}} + b_0 \frac{\partial z_2^*(0,0)}{\partial \bar{\tau}} + d_0 \frac{\partial z_4^*(0,0)}{\partial \bar{\tau}} = 0, \\ e_0 \frac{\partial z_1^*(0,0)}{\partial \bar{\tau}} + f_0 \frac{\partial z_2^*(0,0)}{\partial \bar{\tau}} = 0, \\ i_0 \frac{\partial z_4^*(0,0)}{\partial \bar{\tau}} = 0. \end{cases}$$

That is

$$\begin{cases} \frac{\partial z_1^*(0,0)}{\partial \bar{\tau}} = 0, \\ \frac{\partial z_2^*(0,0)}{\partial \bar{\tau}} = 0, \\ \frac{\partial z_4^*(0,0)}{\partial \bar{\tau}} = 0. \end{cases} \tag{44}$$

In the same way as above, we obtain

$$\begin{cases} \frac{\partial}{\partial \sigma}(\eta_1 - \Theta_1 \circ \Phi(\eta, \eta_1, \eta_2, \eta_3, \eta_4))(0,0) = 0, \\ \frac{\partial}{\partial \sigma}(\eta_2 - \Theta_2 \circ \Phi(\eta, \eta_1, \eta_2, \eta_3, \eta_4))(0,0) = 0, \\ \frac{\partial}{\partial \sigma}(\eta_4 - \Theta_4 \circ \Phi(\eta, \eta_1, \eta_2, \eta_3, \eta_4))(0,0) = 0. \end{cases}$$

Therefore

$$\begin{cases} \frac{\partial z_1^*(0,0)}{\partial \sigma} - \frac{\partial \Theta_1(\Phi(\tau_0,\zeta_0))}{\partial x_0} \left(\frac{\partial \Phi_1(\tau_0,\zeta_0)}{\partial x_0} \left(q_1 + \frac{\partial z_1^*(0,0)}{\partial \sigma} \right) + \frac{\partial \Phi_1(\tau_0,\zeta_0)}{\partial x_1} \left(q_2 + \frac{\partial z_2^*(0,0)}{\partial \sigma} \right) \right. \\ \qquad \left. + \frac{\partial \Phi_1(\tau_0,\zeta_0)}{\partial y_0} + \frac{\partial \Phi_1(\tau_0,\zeta_0)}{\partial y_1} \left(q_1 + \frac{\partial z_4^*(0,0)}{\partial \sigma} \right) \right) = 0, \\ \frac{\partial z_2^*(0,0)}{\partial \sigma} - \frac{\partial \Theta_2(\Phi(\tau_0,\zeta_0))}{\partial x_0} \left(\frac{\partial \Phi_2(\tau_0,\zeta_0)}{\partial x_0} \left(q_1 + \frac{\partial z_1^*(0,0)}{\partial \sigma} \right) + \frac{\partial \Phi_2(\tau_0,\zeta_0)}{\partial x_1} \left(q_2 + \frac{\partial z_2^*(0,0)}{\partial \sigma} \right) \right. \\ \qquad \left. + \frac{\partial \Phi_2(\tau_0,\zeta_0)}{\partial y_0} + \frac{\partial \Phi_2(\tau_0,\zeta_0)}{\partial y_1} \left(q_1 + \frac{\partial z_4^*(0,0)}{\partial \sigma} \right) \right) = 0, \\ \frac{\partial z_4^*(0,0)}{\partial \sigma} - \frac{\partial \Theta_4(\Phi(\tau_0,\zeta_0))}{\partial x_0} \left(\frac{\partial \Phi_4(\tau_0,\zeta_0)}{\partial x_0} \left(q_1 + \frac{\partial z_1^*(0,0)}{\partial \sigma} \right) + \frac{\partial \Phi_4(\tau_0,\zeta_0)}{\partial x_1} \left(q_2 + \frac{\partial z_2^*(0,0)}{\partial \sigma} \right) \right. \\ \qquad \left. + \frac{\partial \Phi_4(\tau_0,\zeta_0)}{\partial y_0} + \frac{\partial \Phi_4(\tau_0,\zeta_0)}{\partial y_1} \left(q_1 + \frac{\partial z_4^*(0,0)}{\partial \sigma} \right) \right) = 0. \end{cases}$$

We obtain

$$\begin{cases} a_0 \frac{\partial z_1^*(0,0)}{\partial \sigma} + b_0 \frac{\partial z_2^*(0,0)}{\partial \sigma} + c_0 + d_0 \frac{\partial z_4^*(0,0)}{\partial \sigma} = 0, \\ e_0 \frac{\partial z_1^*(0,0)}{\partial \sigma} + f_0 \frac{\partial z_2^*(0,0)}{\partial \sigma} = 0, \\ i_0 \frac{\partial z_4^*(0,0)}{\partial \sigma} = 0. \end{cases}$$

That is

$$\begin{cases} \frac{\partial z_1^*(0,0)}{\partial \sigma} = -\frac{f_0 c_0}{a_0 f_0 - b_0 e_0}, \\ \frac{\partial z_2^*(0,0)}{\partial \sigma} = \frac{e_0 c_0}{a_0 f_0 - b_0 e_0}, \\ \frac{\partial z_4^*(0,0)}{\partial \sigma} = 0. \end{cases} \tag{45}$$

4.4. First derivatives of ω

We have

$$\begin{aligned} \frac{\partial \omega}{\partial \bar{\tau}} &= \frac{\partial}{\partial \bar{\tau}}(\eta_3 - \Theta_3 \circ \Phi(\eta, \eta_1, \eta_2, \eta_3, \eta_4)) \\ &= -\frac{\partial \Theta_3}{\partial y_0} \left(\frac{\partial \Phi_3(\eta,\eta_1,\eta_2,\eta_3,\eta_4)}{\partial \bar{\tau}} + \frac{\partial \Phi_3(\eta,\eta_1,\eta_2,\eta_3,\eta_4)}{\partial x_0} \frac{\partial z_1^*}{\partial \bar{\tau}} + \frac{\partial \Phi_3(\eta,\eta_1,\eta_2,\eta_3,\eta_4)}{\partial x_1} \frac{\partial z_2^*}{\partial \bar{\tau}} \right. \\ &\qquad \left. + \frac{\partial \Phi_3(\eta,\eta_1,\eta_2,\eta_3,\eta_4)}{\partial y_1} \frac{\partial z_4^*}{\partial \bar{\tau}} \right). \end{aligned}$$

At $(\bar{\tau}, \sigma) = (0,0)$ we have $\frac{\partial \Phi_3(\tau_0,\zeta_0)}{\partial \bar{\tau}} = 0$, then we obtain

$$\frac{\partial \omega}{\partial \bar{\tau}}(0,0) = -\frac{\partial \Theta_3}{\partial y_0} \left(\frac{\partial \Phi_3(\tau_0,\zeta_0)}{\partial x_0} \frac{\partial z_1^*(0,0)}{\partial \bar{\tau}} + \frac{\partial \Phi_3(\tau_0,\zeta_0)}{\partial x_1} \frac{\partial z_2^*(0,0)}{\partial \bar{\tau}} + \frac{\partial \Phi_3(\tau_0,\zeta_0)}{\partial y_1} \frac{\partial z_4^*(0,0)}{\partial \bar{\tau}} \right) = 0.$$

$$\begin{aligned}\frac{\partial\omega}{\partial\sigma} &= \frac{\partial}{\partial\sigma}(\eta_3 - \Theta_3\circ\Phi(\eta,\eta_1,\eta_2,\eta_3,\eta_4))\\ &= 1-\frac{\partial\Theta_3}{\partial y_0}\left(\frac{\partial\Phi_3(\eta,\eta_1,\eta_2,\eta_3,\eta_4)}{\partial x_0}\left(q_1+\frac{\partial z_1^*}{\partial\sigma}\right)+\frac{\partial\Phi_3(\eta,\eta_1,\eta_2,\eta_3,\eta_4)}{\partial x_1}\left(q_2+\frac{\partial z_2^*}{\partial\sigma}\right)\right.\\ &\qquad\left.+\frac{\partial\Phi_3(\eta,\eta_1,\eta_2,\eta_3,\eta_4)}{\partial y_0}+\frac{\partial\Phi_3(\eta,\eta_1,\eta_2,\eta_3,\eta_4)}{\partial y_1}\left(q_4+\frac{\partial z_4^*}{\partial\sigma}\right)\right).\end{aligned}$$

At $(\bar\tau,\sigma)=(0,0)$ we obtain

$$\begin{aligned}\frac{\partial\omega}{\partial\sigma}(0,0) &= 1-\frac{\partial\Theta_3}{\partial y_0}\left(\frac{\partial\Phi_3(\tau_0,\zeta_0)}{\partial 0_0}\left(q_1+\frac{\partial z_1^*(0,0)}{\partial\sigma}\right)+\frac{\partial\Phi_3(\tau_0,\zeta_0)}{\partial x_1}\left(q_2+\frac{\partial z_2^*(0,0)}{\partial\sigma}\right)\right.\\ &\qquad\left.+\frac{\partial\Phi_3(\tau_0,\zeta_0)}{\partial y_0}+\frac{\partial\Phi_3(\tau_0,\zeta_0)}{\partial y_1}\left(q_4+\frac{\partial z_4^*(0,0)}{\partial\sigma}\right)\right)\\ &= 1-\frac{\partial\Theta_3}{\partial y_0}\frac{\partial\Phi_3(\tau_0,\zeta_0)}{\partial y_0}\\ &= g_0=0\end{aligned}$$

Therefore $D_{(\bar\tau,\sigma)}\omega(0,0)=(0,0)$.

4.5. Second derivatives of ω

Let $\mathcal{A}=\frac{\partial^2\omega(0,0)}{\partial\bar\tau^2}$, $\mathcal{B}=\frac{\partial^2\omega(0,0)}{\partial\bar\tau\partial\sigma}$ and $\mathcal{C}=\frac{\partial^2\omega(0,0)}{\partial\sigma^2}$.

4.5.1. Calculation of $\mathcal{A}$.

We have $\frac{\partial^2\omega}{\partial\bar\tau^2}=\frac{\partial^2}{\partial\bar\tau^2}(\eta_3-\Theta_3\circ\Phi(\eta,\eta_1,\eta_2,\eta_3,\eta_4))$, then

$$\begin{aligned}\frac{\partial^2\omega}{\partial\bar\tau^2} &= -\frac{\partial\Theta_3}{\partial y_0}\left\{\frac{\partial^2\Phi_3(\eta,\eta_1,\eta_2,\eta_3,\eta_4)}{\partial\bar\tau^2}+2\frac{\partial^2\Phi_3(\eta,\eta_1,\eta_2,\eta_3,\eta_4)}{\partial\bar\tau\partial x_0}\frac{\partial z_1^*}{\partial\bar\tau}+2\frac{\partial^2\Phi_3(\eta,\eta_1,\eta_2,\eta_3,\eta_4)}{\partial\bar\tau\partial x_1}\frac{\partial z_2^*}{\partial\bar\tau}\right.\\ &+2\frac{\partial^2\Phi_3(\eta,\eta_1,\eta_2,\eta_3,\eta_4)}{\partial\bar\tau\partial y_1}\frac{\partial z_4^*}{\partial\bar\tau}+\frac{\partial^2\Phi_3(\eta,\eta_1,\eta_2,\eta_3,\eta_4)}{\partial x_0^2}\left(\frac{\partial z_1^*}{\partial\bar\tau}\right)^2+2\frac{\partial^2\Phi_3(\eta,\eta_1,\eta_2,\eta_3,\eta_4)}{\partial x_0\partial x_1}\frac{\partial z_1^*}{\partial\bar\tau}\frac{\partial z_2^*}{\partial\bar\tau}\\ &+2\frac{\partial^2\Phi_3(\eta,\eta_1,\eta_2,\eta_3,\eta_4)}{\partial x_0\partial y_1}\frac{\partial z_1^*}{\partial\bar\tau}\frac{\partial z_4^*}{\partial\bar\tau}+\frac{\partial\Phi_3(\eta,\eta_1,\eta_2,\eta_3,\eta_4)}{\partial x_0}\frac{\partial^2 z_1^*}{\partial\bar\tau^2}+\frac{\partial^2\Phi_3(\eta,\eta_1,\eta_2,\eta_3,\eta_4)}{\partial x_1^2}\left(\frac{\partial z_2^*}{\partial\bar\tau}\right)^2\\ &+2\frac{\partial^2\Phi_3(\eta,\eta_1,\eta_2,\eta_3,\eta_4)}{\partial x_1\partial y_1}\frac{\partial z_2^*}{\partial\bar\tau}\frac{\partial z_4^*}{\partial\bar\tau}+\frac{\partial\Phi_3(\eta,\eta_1,\eta_2,\eta_3,\eta_4)}{\partial x_1}\frac{\partial^2 z_2^*}{\partial\bar\tau^2}+\frac{\partial^2\Phi_3(\eta,\eta_1,\eta_2,\eta_3,\eta_4)}{\partial y_1^2}\left(\frac{\partial z_4^*}{\partial\bar\tau}\right)^2\\ &\left.+\frac{\partial\Phi_3(\eta,\eta_1,\eta_2,\eta_3,\eta_4)}{\partial y_1}\frac{\partial^2 z_4^*}{\partial\bar\tau^2}\right\}.\end{aligned}$$

At $(\bar\tau,\sigma)=(0,0)$ we have $\frac{\partial^2\Phi_3(\tau_0,\zeta_0)}{\partial\bar\tau^2}=0$. Then

$$\mathcal{A}=0.$$

4.5.2. Calculation of $\mathcal{C}$.

We have $\frac{\partial^2\omega}{\partial\sigma^2}=\frac{\partial^2}{\partial\sigma^2}(\eta_3-\Theta_3\circ\Phi(\eta,\eta_1,\eta_2,\eta_3,\eta_4))$, then

$$\begin{aligned}\frac{\partial^2\omega}{\partial\sigma^2} = &-\frac{\partial\Theta_3}{\partial y_0}\left(\frac{\partial^2\Phi_3(\eta,\eta_1,\eta_2,\eta_3,\eta_4)}{\partial x_0^2}\left(q_1+\frac{\partial z_1^*}{\partial\sigma}\right)^2+2\frac{\partial^2\Phi_3(\eta,\eta_1,\eta_2,\eta_3,\eta_4)}{\partial x_0\partial x_1}\left(q_1+\frac{\partial z_1^*}{\partial\sigma}\right)\left(q_2+\frac{\partial z_2^*}{\partial\sigma}\right)\right.\\ &+2\frac{\partial^2\Phi_3(\eta,\eta_1,\eta_2,\eta_3,\eta_4)}{\partial x_0\partial y_1}\left(q_1+\frac{\partial z_1^*}{\partial\sigma}\right)\left(q_4+\frac{\partial z_4^*}{\partial\sigma}\right)+2\frac{\partial^2\Phi_3(\eta,\eta_1,\eta_2,\eta_3,\eta_4)}{\partial x_0\partial y_0}\left(q_1+\frac{\partial z_1^*}{\partial\sigma}\right)\\ &+\frac{\partial\Phi_3(\eta,\eta_1,\eta_2,\eta_3,\eta_4)}{\partial x_0}\left(\frac{\partial^2 z_1^*}{\partial\sigma^2}\right)+\frac{\partial^2\Phi_3(\eta,\eta_1,\eta_2,\eta_3,\eta_4)}{\partial x_1^2}\left(q_2+\frac{\partial z_2^*}{\partial\sigma}\right)^2\\ &+2\frac{\partial^2\Phi_3(\eta,\eta_1,\eta_2,\eta_3,\eta_4)}{\partial x_1\partial y_1}\left(q_2+\frac{\partial z_2^*}{\partial\sigma}\right)\left(q_4+\frac{\partial z_4^*}{\partial\sigma}\right)+2\frac{\partial^2\Phi_3(\eta,\eta_1,\eta_2,\eta_3,\eta_4)}{\partial y_0\partial x_1}\left(q_2+\frac{\partial z_2^*}{\partial\sigma}\right)\\ &+\frac{\partial\Phi_3(\eta,\eta_1,\eta_2,\eta_3,\eta_4)}{\partial x_1}\left(\frac{\partial^2 z_2^*}{\partial\sigma^2}\right)+\frac{\partial^2\Phi_3(\eta,\eta_1,\eta_2,\eta_3,\eta_4)}{\partial y_1^2}\left(\frac{\partial z_4^*}{\partial\sigma}\right)^2+2\frac{\partial^2\Phi_3(\eta,\eta_1,\eta_2,\eta_3,\eta_4)}{\partial y_0\partial y_1}\left(q_4+\frac{\partial z_4^*}{\partial\sigma}\right)\\ &\left.+\frac{\partial\Phi_3(\eta,\eta_1,\eta_2,\eta_3,\eta_4)}{\partial y_1}\left(\frac{\partial^2 z_4^*}{\partial\sigma^2}\right)+\frac{\partial^2\Phi_3(\eta,\eta_1,\eta_2,\eta_3,\eta_4)}{\partial y_0^2}\right\}.\end{aligned}$$

At $(\bar{\tau},\sigma)=(0,0)$ we obtain

$$\begin{aligned}\mathcal{C} &= -\frac{\partial\Theta_3}{\partial y_0}\left\{2\frac{\partial^2\Phi_3(\tau_0,\zeta_0)}{\partial x_0\partial y_0}\left(q_1+\frac{\partial z_1^*(0,0)}{\partial\sigma}\right)+2\frac{\partial^2\Phi_3(\tau_0,\zeta_0)}{\partial x_1\partial y_0}\left(q_2+\frac{\partial z_2^*(0,0)}{\partial\sigma}\right)\right.\\ &\left.+2\frac{\partial^2\Phi_3(\tau_0,\zeta_0)}{\partial y_0\partial y_1}q_4+\frac{\partial^2\Phi_3(\tau_0,\zeta_0)}{\partial y_0^2}\right\}.\end{aligned}$$

4.5.3. Calculation of $\mathcal{B}$.

We have $\frac{\partial^2\omega}{\partial\bar{\tau}\partial\sigma}=\frac{\partial}{\partial\bar{\tau}}\left(\frac{\partial}{\partial\sigma}(\eta_3-\Theta_3\circ\Phi(\eta,\eta_1,\eta_2,\eta_3,\eta_4))\right)$, then

$$\begin{aligned}\frac{\partial^2\omega}{\partial\bar{\tau}\partial\sigma} = & -\frac{\partial\Theta_3}{\partial y_0}\left\{\frac{\partial^2\Phi_3(\eta,\eta_1,\eta_2,\eta_3,\eta_4)}{\partial\bar{\tau}\partial x_0}\left(q_1+\frac{\partial z_1^*}{\partial\sigma}\right)+\frac{\partial^2\Phi_3(\eta,\eta_1,\eta_2,\eta_3,\eta_4)}{\partial\bar{\tau}\partial x_1}\left(q_2+\frac{\partial z_2^*}{\partial\sigma}\right)\right.\\ & +\frac{\partial^2\Phi_3(\eta,\eta_1,\eta_2,\eta_3,\eta_4)}{\partial\bar{\tau}\partial y_0}+\frac{\partial^2\Phi_3(\eta,\eta_1,\eta_2,\eta_3,\eta_4)}{\partial\bar{\tau}\partial y_1}\left(q_4+\frac{\partial z_4^*}{\partial\sigma}\right)\\ & +\frac{\partial^2\Phi_3(\eta,\eta_1,\eta_2,\eta_3,\eta_4)}{\partial x_0^2}\frac{\partial z_1^*}{\partial\bar{\tau}}\left(q_1+\frac{\partial z_1^*}{\partial\sigma}\right)+\frac{\partial^2\Phi_3(\eta,\eta_1,\eta_2,\eta_3,\eta_4)}{\partial x_0\partial x_1}\frac{\partial z_1^*}{\partial\bar{\tau}}\left(q_2+\frac{\partial z_2^*}{\partial\sigma}\right)\\ & +\frac{\partial^2\Phi_3(\eta,\eta_1,\eta_2,\eta_3,\eta_4)}{\partial y_0\partial x_0}\frac{\partial z_1^*}{\partial\bar{\tau}}+\frac{\partial^2\Phi_3(\eta,\eta_1,\eta_2,\eta_3,\eta_4)}{\partial y_1\partial x_0}\frac{\partial z_1^*}{\partial\bar{\tau}}\left(q_4+\frac{\partial z_4^*}{\partial\sigma}\right)\\ & +\frac{\partial\Phi_3(\eta,\eta_1,\eta_2,\eta_3,\eta_4)}{\partial x_0}\frac{\partial^2 z_1^*}{\partial\bar{\tau}\partial\sigma}+\frac{\partial^2\Phi_3(\eta,\eta_1,\eta_2,\eta_3,\eta_4)}{\partial x_0\partial x_1}\frac{\partial z_2^*}{\partial\bar{\tau}}\left(q_1+\frac{\partial z_1^*}{\partial\sigma}\right)\\ & +\frac{\partial^2\Phi_3(\eta,\eta_1,\eta_2,\eta_3,\eta_4)}{\partial x_1^2}\frac{\partial z_2^*}{\partial\bar{\tau}}\left(q_2+\frac{\partial z_2^*}{\partial\sigma}\right)+\frac{\partial^2\Phi_3(\eta,\eta_1,\eta_2,\eta_3,\eta_4)}{\partial x_1\partial y_0}\frac{\partial z_2^*}{\partial\bar{\tau}}\\ & +\frac{\partial^2\Phi_3(\eta,\eta_1,\eta_2,\eta_3,\eta_4)}{\partial x_1\partial y_1}\frac{\partial z_2^*}{\partial\bar{\tau}}\left(q_4+\frac{\partial z_4^*}{\partial\sigma}\right)+\frac{\partial\Phi_3(\eta,\eta_1,\eta_2,\eta_3,\eta_4)}{\partial x_1}\frac{\partial^2 z_2^*}{\partial\bar{\tau}\partial\sigma}\\ & +\frac{\partial^2\Phi_3(\eta,\eta_1,\eta_2,\eta_3,\eta_4)}{\partial y_1\partial x_0}\frac{\partial z_4^*}{\partial\bar{\tau}}\left(q_1+\frac{\partial z_1^*}{\partial\sigma}\right)+\frac{\partial^2\Phi_3(\eta,\eta_1,\eta_2,\eta_3,\eta_4)}{\partial y_1\partial x_1}\frac{\partial z_4^*}{\partial\bar{\tau}}\left(q_2+\frac{\partial z_2^*}{\partial\sigma}\right)\\ & +\frac{\partial^2\Phi_3(\eta,\eta_1,\eta_2,\eta_3,\eta_4)}{\partial y_1^2}\frac{\partial z_1^*}{\partial\bar{\tau}}\left(q_4+\frac{\partial z_4^*}{\partial\sigma}\right)+\frac{\partial^2\Phi_3(\eta,\eta_1,\eta_2,\eta_3,\eta_4)}{\partial y_0\partial y_1}\frac{\partial z_4^*}{\partial\bar{\tau}}\\ & \left.+\frac{\partial\Phi_3(\eta,\eta_1,\eta_2,\eta_3,\eta_4)}{\partial y_1}\frac{\partial^2 z_4^*}{\partial\bar{\tau}\partial\sigma}\right\}.\end{aligned}$$

At $(\bar{\tau},\sigma)=(0,0)$ we have $\frac{\partial^2\Phi_3(\tau_0,\zeta_0)}{\partial\bar{\tau}\partial x_0}=\frac{\partial^2\Phi_3(\tau_0,\zeta_0)}{\partial\bar{\tau}\partial x_1}=\frac{\partial^2\Phi_3(\tau_0,\zeta_0)}{\partial\bar{\tau}\partial y_1}=0$, then we obtain

$$\mathcal{B}=-\frac{\partial\Theta_3}{\partial y_0}\frac{\partial^2\Phi_3(\tau_0,\zeta_0)}{\partial\bar{\tau}\partial y_0}.$$

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