

EFFICIENT NUMERICAL METHOD FOR A MODEL ARISING IN BIOLOGICAL STOICHIOMETRY OF TUMOUR DYNAMICS

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ABSTRACT. In this paper, we extend a system of coupled first order non-linear system of delay differential equations (DDEs) arising in modeling of stoichiometry of tumour dynamics, to a system of diffusion-reaction system of partial delay differential equations (PDDEs). Since tumor cells is further modified by blood supply through the vascularization process, thus we determine the local uniform steady states of the homogeneous tumour growth model with respect to the vascularization process. We show that the steady states are globally stable, determine the existence of Hopf bifurcation of the homogeneous tumour growth model with respect to the vascularization process. We derive, analyse and implement a fitted operator finite difference method (FOFDM) to solve the extended model. This FOFDM is analyzed for convergence and it is seen that it has second-order accuracy. Some numerical results confirming theoretical observations are also presented. These results are comparable with those obtained in the literature.

1. Introduction. When a body develops a disease, the situation can be thought similar to that of predator and prey in ecology. However some diseases are very much complex in their formation and the manner they reinforce their presence in a body as compare to a situation in a physical environment. Such diseases are for example HIV and cancer. In this paper we focus on a tumour. Therefore when a host is affected by a tumour, the system requires interaction with its environment. Therefore, it is not strange for the ecological system of cancer cells to interacts with surrounding cells, both healthy and malignant. This means cancer and healthy cells should compete for resources, and these are oxygen, nutrient and space. Thus cancer cells compete against each others and against the healthy cells throughout the body for the same resources. It is this competition that necessitates the consideration of the effects of biological stoichiometry to supplement the first principles of malignant tumours' cells [7]. Similar considerations of biological stoichiometry can be found in [4, 5, 23]. In this paper, we consider the biological stoichiometry derived in [7].

In [7], it is established that the qualitative dynamics of the models are essentially unchanged whether phosphorus limits blood vessel construction or not. Thus, Elser et al. [7] claimed that varying the supply of phosphorus continuously seems to

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create no new dynamical behavior. Therefore, this motivated us to investigate the extended homogeneous tumour growth model directly.

This implies that, our first aim in this paper is to investigate the qualitative features of the model with regard to blood vessel construction and determine the possibility of the time delay τ on the dynamics of the homogeneous tumour growth model. By applying the Poincaré normal form and center manifold theorem [8, 24], we determine conditions on the functions and derive formulas which determine the properties of Hopf bifurcation [19] such as the direction of bifurcation, the period of periodic solutions and the stability of solutions. More specifically, we show that the positive equilibrium point loses its stability and the system exhibits Hopf bifurcation under certain conditions.

Our second aim is to solve the extended model. Thus, we develop an efficient numerical method for solving the extended model with respect to the qualitative features of the extended model. To this end we highlight our motivation for our numerical method. The deficiencies of the standard finite difference methods in solving the problems like the one in equation (2) are well-known. While explicit methods can solve such differential equations with low computational cost, they have the drawback that their stability regions are very small. This implies severe restrictions on the time and space step-sizes will be required in order to achieve satisfactorily converging results. On the other hand, an implicit schemes do have wider stability regions but the associated computational complexity is very high and they cannot achieve more than one order as compared to explicit methods that use the same number of stages [3].

When a single solid tumour is growing within an organ Elser et al. [7] mentioned that the initial mass starts near some genetically determined carrying capacity (k_h) and its vascularization process takes place at approximately 0.01kg. Since the parenchyma cells may contain distinct cell types that differ in their nutrient use and growth rates, then Elser et al. [7] developed the heterogeneous tumor model with dietary regulation as

$$\left. \begin{aligned} \frac{dx}{dt} &= x \left(a \min \left(1, \frac{P_e}{fnk_h} \right) - d_x - (a - d_x) \frac{x+y_1+y_2+z}{k_h} \right), \\ \frac{dy_1}{dt} &= y_1 \left(b_1 \min \left(1, \beta \frac{P_e}{fmk_h} \right) \min(1, L) - d_1 - (b_1 - d_1) \frac{y_1+y_2+z}{k_t} \right), \\ \frac{dy_2}{dt} &= y \left(b_2 \min \left(1, \beta \frac{P_e}{fmk_h} \right) \min(1, L) - d_2 - (b_2 - d_2) \frac{y_1+y_2+z}{k_t} \right), \\ \frac{dz}{dt} &= c \min \left(1, \frac{P_e}{fnk_h} \right) (y_1(t - \tau) + y_2(t - \tau)) - d_z z, \\ \frac{dP}{dt} &= r - \gamma \left(n(d_x x + d_z z) + (a - d_x) n x \frac{x+y_1+y_2+z}{k_h} \right) \\ &\quad - \gamma \left(\sum_{i=1}^2 m_i d_i y_i + \frac{y_1+y_2+z}{k_t} \sum_{i=1}^2 m_i (b_i - d_i) \right), \\ L &= g \frac{z - \alpha(y_1+y_2)}{y_1+y_2}, \\ P_e &\equiv P(t) - nx - m_1 y_1 - m_2 y_2 - nz, \end{aligned} \right\} \quad (1)$$

where x , y_i ($i = 1, 2$ in this case), z , f , β , P_e , P , L , n and m_i denote mass of healthy cells, tumour mass contributed by the i^{th} parenchyma cell type, mass of tumour micro-vessels, fraction of the total fluid within an organ, therapeutic intervention, extracellular phosphorus within the organ, the homeostatic regulation of the total amount of phosphorus, maximum proliferation rate of tumour cells, the mean amount of phosphorus in healthy cells and mean amount of phosphorus in

parenchyma cells in that order. The cells proliferation and death at maximum per capita rates are denoted by a, b_i and d_x, d_i , respectively, whereas α and g denote mass of cancer cells of which one unit of blood vessels can barely maintain and measurements of sensitivity of tumour tissue due to lack blood.

The model in equation (1) is a system of first order delay differential equations (DDEs), therefore initial values are required by the system. Elser et al. [7] provided the initial conditions as $(x(0), y_1(0), y_2(0), z(0)) = (9.00, 0.01, 0.01, 0.001)$, and did not give the initial condition for $P(0)$.

When a tumour has only one parenchyma cell type then the system of first order delay differential equations in equations (DDEs) (1) is known as homogeneous tumour growth model and heterogeneous tumour growth model when a tumour has more than one parenchyma cell type.

As we see, all of the above models did not take spatial effects into account. In fact, cells can move around subject to many factors including diffusion. Thus, instead of depicting the models with purely time dependent ordinary differential equations (ODEs) with delay, it is more realistic to introduce the diffusion of the cells into the system, and the simplest way to reach this goal is to use the concept of reaction-diffusion equations [10, 11]. Elser et al., [7] showed that at a steady state, tumor growth is no longer limited by its blood vessel infrastructure. For that reason, they also found out that when the tumor is viewed as a single entity, the homogeneous and heterogeneous models essentially generate the same dynamics. Thus, in this paper we consider the homogeneous tumor growth model. Therefore, incorporating spatial effects into equation (1), the homogeneous tumour growth model in (1) becomes

$$\left. \begin{aligned} \frac{\partial X}{\partial t} - \mathcal{D}_x \Delta X &= X \left(a \min \left(1, \frac{P_e}{f n k_h} \right) - d_x - (a - d_x) \frac{X + Y_1 + Z}{k_h} \right), \\ \frac{\partial Y_1}{\partial t} - \mathcal{D}_{y_1} \Delta Y_1 &= Y_1 \left(b_1 \min \left(1, \beta \frac{P_e}{f m k_h} \right) \min(1, L) - d_1 - (b_1 - d_1) \frac{Y_1 + Z}{k_t} \right), \\ \frac{\partial Z}{\partial t} - \mathcal{D}_z \Delta Z &= c \min \left(1, \frac{P_e}{f n k_h} \right) Y_1(t - \tau) - d_z Z, \quad L = g \frac{Z - \alpha Y_1}{Y_1}, \\ P_e &\equiv P - nX - m_1 Y_1 - nZ, \quad \text{on } (x, t) \in \Omega \times (0, \infty), \\ \frac{\partial X}{\partial \nu}(0, t) = \frac{\partial Y_1}{\partial \nu}(0, t) = \frac{\partial Z}{\partial \nu}(0, t) &= 0, \quad \text{on } (x, t) \in \Omega \times (0, \infty), \\ \frac{\partial X}{\partial \nu}(x_f, t) = \frac{\partial Y_1}{\partial \nu}(x_f, t) = \frac{\partial Z}{\partial \nu}(x_f, t) &= 0, \quad \text{on } (x, t) \in \Omega \times (0, \infty), \\ \mathcal{X}_j(x, 0) = \eta_j(x), \quad \text{on } (x, t) \in \bar{\Omega} \times [-\tau, 0], \quad j &= 1, 2, 3. \end{aligned} \right\} \quad (2)$$

where Δ denotes the Laplace operator, $\mathcal{X}_j(x, t) = [X, Y_1, Z]$, $\Omega \in \mathbb{R}^3$ denotes a bounded domain with smooth boundary $\partial\Omega$ and ν denotes the outward unit normal on $\partial\Omega$. The initial function $\eta_j(x, t)$ is Holder continuous on $[-\tau, 0]$ [18]. We imposed the no flux-boundary conditions in order to ensure that we exclude the external effects.

The rest of the paper is as follows, Section 2 we analyse the steady state and existence of Hopf bifurcation analysis for two possible blood limiting cases. We derive, analyse our numerical method in Section 3 and present our numerical results in Section 4 and conclude the paper with Section 5.

2. Mathematical analysis of the homogeneous tumour growth model. To proceed, we recall from Elser et al. in [7], that in a phosphorus-rich environment, healthy cells and tumor cells can proliferate, however, if the extracellular phosphorus

concentration drops below a threshold value, then the growth rates of both healthy and tumor cells are impaired. Therefore, in such case we let

$$\varphi_{P_x} := \min\left(1, \frac{P_e}{fnk_h}\right), \varphi_{P_{y_1}} := \min\left(1, \beta \frac{P_e}{fm_1k_h}\right), \varphi_{P_z} := \min\left(1, \frac{P_e}{fnk_h}\right), \tag{3}$$

to denote such possibilities of limitations. Since maximum proliferation rate of tumour cells is dictated by the value of $\min\left(1, g \frac{Z-\alpha Y_1}{Y_1}\right)$ [7], then, at the steady state, the homogeneous tumour growth model in equation (2) becomes

$$\left. \begin{aligned} X \left(a\varphi_{P_x} - d_x - (a - d_x) \frac{X+Y_1+Z}{k_h} \right) &= 0, \\ Y_1 \left(b_1\varphi_{P_{y_1}} \min\left(1, g \frac{Z-\alpha Y_1}{Y_1}\right) - d_1 - (b_1 - d_1) \frac{Y_1+Z}{k_t} \right) &= 0, \\ c\varphi_{P_z} Y_1 - d_z Z &= 0, \end{aligned} \right\} \tag{4}$$

which gives the trivial equilibrium point $(0, 0, 0)$, and the system

$$\left. \begin{aligned} \frac{(a-d_x)}{k_h} (X + Y_1 + Z) &= a\varphi_{P_x} - d_x, \\ \frac{(b_1-d_1)}{k_t} (Y_1 + Z) &= b_1\varphi_{P_{y_1}} - d_1, \\ c\varphi_{P_z} Y_1 - d_z Z &= 0, \end{aligned} \right\} \tag{5}$$

if $\min\left(1, g \frac{Z-\alpha Y_1}{Y_1}\right) = 1$ and

$$\left. \begin{aligned} \frac{(a-d_x)}{k_h} (X + Y_1 + Z) &= a\varphi_{P_x} - d_x, \\ \frac{(b_1-d_1)}{k_t} (Y_1 + Z) - b_1\varphi_{P_{y_1}} g \frac{Z-\alpha Y_1}{Y_1} &= -d_1, \\ c\varphi_{P_z} Y_1 - d_z Z &= 0, \end{aligned} \right\} \tag{6}$$

if $\min\left(1, g \frac{Z-\alpha Y_1}{Y_1}\right) \neq 1$. Thus, we consider both cases in the next two sections.

2.1. Local stability for $\min\left(1, g \frac{Z-\alpha Y_1}{Y_1}\right) = 1$. When $\min\left(1, g \frac{z-\alpha Y_1}{Y_1}\right) = 1$ equation (5) is equivalent to

$$\begin{pmatrix} \frac{(a-d_x)}{k_h} & \frac{(a-d_x)}{k_h} & \frac{(a-d_x)}{k_h} \\ 0 & \frac{(b_1-d_1)}{k_t} & \frac{(b_1-d_1)}{k_t} \\ 0 & c\varphi_{P_z} & -d_z \end{pmatrix} \begin{pmatrix} X \\ Y_1 \\ Z \end{pmatrix} = \begin{pmatrix} a\varphi_{P_x} - d_x \\ b_1\varphi_{P_{y_1}} - d_1 \\ 0 \end{pmatrix}, \tag{7}$$

and the determinant of the matrix in equation (7) is

$$\frac{(a - d_x)}{k_h} \begin{vmatrix} \frac{(b_1-d_1)}{k_t} & \frac{(b_1-d_1)}{k_t} \\ c\varphi_{P_z} & -d_z \end{vmatrix} = -\frac{(a - d_x)}{k_h} \frac{(b_1 - d_1)}{k_t} (d_z + c\varphi_{P_z}), \tag{8}$$

provided that $a > d_x$, $a\varphi_{P_x} > d_x$ and $b_1 \neq d_1$. Thus,

$$X^* = \frac{\begin{vmatrix} a\varphi_{P_x} - d_x & \frac{(a-d_x)}{k_h} & \frac{(a-d_x)}{k_h} \\ b_1\varphi_{P_{y_1}} - d_1 & \frac{(b_1-d_1)}{k_t} & \frac{(b_1-d_1)}{k_t} \\ 0 & c\varphi_{P_z} & -d_z \end{vmatrix}}{-\frac{(a-d_x)}{k_h} \frac{(b_1-d_1)}{k_t} (d_z + c\varphi_{P_z})}, \tag{9}$$

where the determinant of the numerator in equation (9) is

$$\begin{aligned}
& \begin{vmatrix} a\varphi_{P_x} - d_x & \frac{(a-d_x)}{k_h} & \frac{(a-d_x)}{k_h} \\ b_1\varphi_{P_{y_1}} - d_1 & \frac{(b_1-d_1)}{k_t} & \frac{(b_1-d_1)}{k_t} \\ 0 & c\varphi_{P_z} & -d_z \end{vmatrix} \\
&= (a\varphi_{P_x} - d_x) \begin{vmatrix} \frac{(b_1-d_1)}{k_t} & \frac{(b_1-d_1)}{k_t} \\ c\varphi_{P_z} & -d_z \end{vmatrix} \\
&\quad - \frac{(a-d_x)}{k_h} \begin{vmatrix} b_1\varphi_{P_{y_1}} - d_1 & \frac{(b_1-d_1)}{k_t} \\ 0 & -d_z \end{vmatrix} \\
&\quad + \frac{(a-d_x)}{k_h} \begin{vmatrix} b_1\varphi_{P_{y_1}} - d_1 & \frac{(b_1-d_1)}{k_t} \\ 0 & c\varphi_{P_z} \end{vmatrix}, \\
&= -\frac{(b_1-d_1)}{k_t} (a\varphi_{P_x} - d_x) [d_z + c\varphi_{P_z}] \\
&\quad + \frac{(a-d_x)}{k_h} (b_1\varphi_{P_{y_1}} - d_1) [d_z + c\varphi_{P_z}], \\
&= (d_z + c\varphi_{P_z}) \left(\frac{(a-d_x)(b_1\varphi_{P_{y_1}} - d_1)}{k_h} \right. \\
&\quad \left. - \frac{(b_1-d_1)(a\varphi_{P_x} - d_x)}{k_t} \right).
\end{aligned}$$

Therefore, equation (9) becomes

$$\begin{aligned}
X^* &= \frac{(d_z + c\varphi_{P_z}) \left(\frac{(a-d_x)(b_1\varphi_{P_{y_1}} - d_1)}{k_h} - \frac{(b_1-d_1)(a\varphi_{P_x} - d_x)}{k_t} \right)}{-\frac{(a-d_x)}{k_h} \frac{(b_1-d_1)}{k_t} (d_z + c\varphi_{P_z})}, \\
&= \frac{\left(\frac{(a-d_x)(b_1\varphi_{P_{y_1}} - d_1)}{k_h} - \frac{(b_1-d_1)(a\varphi_{P_x} - d_x)}{k_t} \right)}{-\frac{(a-d_x)}{k_h} \frac{(b_1-d_1)}{k_t}}, \\
&= \frac{k_h(a\varphi_{P_x} - d_x)}{(a-d_x)} - \frac{k_t(b_1\varphi_{P_{y_1}} - d_1)}{(b_1-d_1)},
\end{aligned}$$

provided that $\frac{k_h(a\varphi_{P_x}-d_x)}{(a-d_x)} > \frac{k_t(b_1\varphi_{P_{y_1}}-d_1)}{(b_1-d_1)}$. For Y_1^* , we then have from equations in (7-8) that

$$\begin{aligned} Y_1^* &= \frac{\begin{vmatrix} \frac{(a-d_x)}{k_h} & a\varphi_{P_x}-d_x & \frac{(a-d_x)}{k_h} \\ 0 & b_1\varphi_{P_{y_1}}-d_1 & \frac{(b_1-d_1)}{k_t} \\ 0 & 0 & -d_z \end{vmatrix}}{-\frac{(a-d_x)}{k_h}\frac{(b_1-d_1)}{k_t}(d_z+c\varphi_{P_z})} = \frac{-d_z\frac{(a-d_x)(b_1\varphi_{P_{y_1}}-d_1)}{k_h}}{-\frac{(a-d_x)}{k_h}\frac{(b_1-d_1)}{k_t}(d_z+c\varphi_{P_z})}, \\ &= \frac{k_t d_z (b_1 \varphi_{P_{y_1}} - d_1)}{(b_1 - d_1)(d_z + c\varphi_{P_z})}, \end{aligned}$$

provided that $b_1 > d_1$ and $b_1\varphi_{P_{y_1}} > d_1$. Similarly for Z^* , from equations in (7-8) we have

$$Z^* = \frac{\begin{vmatrix} \frac{(a-d_x)}{k_h} & \frac{(a-d_x)}{k_h} & a\varphi_{P_x}-d_x \\ 0 & \frac{(b_1-d_1)}{k_t} & b_1\varphi_{P_{y_1}}-d_1 \\ 0 & c\varphi_{P_z} & 0 \end{vmatrix}}{-\frac{(a-d_x)}{k_h}\frac{(b_1-d_1)}{k_t}(d_z+c\varphi_{P_z})} = \frac{ck_t\varphi_{P_z}(b_1\varphi_{P_{y_1}}-d_1)}{(b_1-d_1)(d_z+c\varphi_{P_z})}, \quad (10)$$

which requires $b_1 > d_1$ and $b_1\varphi_{P_{y_1}} > d_1$, as anticipated. Therefore, we have two positive equilibrium points and they are

$$\mathcal{E}_1 := \begin{pmatrix} k_h \frac{a\varphi_{P_x}-d_x}{(a-d_x)} \\ 0 \\ 0 \end{pmatrix} \text{ and } \mathcal{E}_2 := \begin{pmatrix} \frac{k_h(a\varphi_{P_x}-d_x)}{(a-d_x)} - \frac{k_t(b_1\varphi_{P_{y_1}}-d_1)}{(b_1-d_1)} \\ \frac{k_t d_z (b_1 \varphi_{P_{y_1}} - d_1)}{(b_1 - d_1)(d_z + c\varphi_{P_z})} \\ \frac{ck_t\varphi_{P_z}(b_1\varphi_{P_{y_1}}-d_1)}{(b_1-d_1)(d_z+c\varphi_{P_z})} \end{pmatrix}. \quad (11)$$

This gives us the following results.

Theorem 2.1. *When $\min\left(1, g^{\frac{Z-\alpha Y_1}{Y_1}}\right) = 1$ and the following conditions*

- (i) $a > d_x$,
- (ii) $a\varphi_{P_x} > d_x$,
- (iii) $\frac{k_h(a\varphi_{P_x}-d_x)}{(a-d_x)} > \frac{k_t(b_1\varphi_{P_{y_1}}-d_1)}{(b_1-d_1)}$,
- (iv) $b_1\varphi_{P_{y_1}} > d_1$,

the homogeneous tumour growth model in equation (2) possess the unique semi-trivial non-negative constant solution $(X^, Y_1^*, Z^*) = (k_h \frac{a\varphi_{P_x}-d_x}{(a-d_x)}, 0, 0)$ and a unique positive constant solution*

$$(X^*, Y_1^*, Z^*) = \begin{pmatrix} \frac{k_h(a\varphi_{P_x}-d_x)}{(a-d_x)} - \frac{k_t(b_1\varphi_{P_{y_1}}-d_1)}{(b_1-d_1)} \\ \frac{k_t d_z (b_1 \varphi_{P_{y_1}} - d_1)}{(b_1 - d_1)(d_z + c\varphi_{P_z})} \\ \frac{ck_t\varphi_{P_z}(b_1\varphi_{P_{y_1}}-d_1)}{(b_1-d_1)(d_z+c\varphi_{P_z})} \end{pmatrix}. \quad (12)$$

Therefore, when the maximum proliferation rate of tumor cells greater than unity, then the steady states are positive as long as the genetically determined, carrying capacity for healthy cells is bigger than that of the tumour cells.

2.2. **Local stability for $\min\left(1, g \frac{Z-\alpha Y_1}{Y_1}\right) \neq 1$.** From equation (6) we have a system of non-linear equations as

$$\left. \begin{aligned} \frac{(a-d_x)}{k_h}(X + Y_1 + Z) &= a\varphi_{P_x} - d_x, \\ b_1\varphi_{P_{y_1}}gZ - (g\alpha - d_1)Y_1 - (b_1 - d_1)\frac{Y_1^2 + Y_1Z}{k_t} &= 0 \\ c\varphi_{P_z}Y_1 - d_zZ &= 0. \end{aligned} \right\} \quad (13)$$

From the last equation in (13), we have $Z = \frac{c\varphi_{P_z}}{d_z}Y_1$. Substituting $Z = \frac{c\varphi_{P_z}}{d_z}Y_1$ into the first and second equation in (13), we obtain

$$\left. \begin{aligned} \frac{(a-d_x)}{k_h}X + \left(\frac{(a-d_x)}{k_h} + \frac{c\varphi_{P_z}}{d_z}\right)Y_1 &= a\varphi_{P_x} - d_x, \\ \left(b_1\varphi_{P_{y_1}}g\frac{c\varphi_{P_z}}{d_z} - (g\alpha - d_1)\right)Y_1 - (b_1 - d_1)\frac{(1+c\varphi_{P_z})}{d_z k_t}Y_1^2 &= 0, \end{aligned} \right\} \quad (14)$$

from which we obtain $Y_1^* = 0$ and $Y_1^* = \frac{(b_1\varphi_{P_{y_1}}g\frac{c\varphi_{P_z}}{d_z} - (g\alpha - d_1))}{(b_1 - d_1)\frac{(1+c\varphi_{P_z})}{d_z k_t}}$. When $Y_1^* = 0$, we obtain a trivial steady state solution $(X^*, Y_1^*, Z^*) = (0, 0, 0)$. However, for non-zero Y_1^* , we find

$$\left. \begin{aligned} X^* &= \frac{k_h(a\varphi_{P_x} - d_x)}{(a-d_x)} - \left(1 + \frac{c\varphi_{P_z}}{d_z}\right)\frac{(b_1\varphi_{P_{y_1}}g\frac{c\varphi_{P_z}}{d_z} - (g\alpha - d_1))}{(b_1 - d_1)\frac{(1+c\varphi_{P_z})}{d_z k_t}}, \\ Z^* &= \frac{c\varphi_{P_z}}{d_z}Y_1^*. \end{aligned} \right\} \quad (15)$$

Thus, we see that if $b_1\varphi_{P_{y_1}}g\frac{c\varphi_{P_z}}{d_z} > (g\alpha - d_1)$ then Y_1^* is positive as $b_1 > d_1$. This implies that $Z^* = \frac{c\varphi_{P_z}}{d_z}Y_1^*$ is positive too. We also see that $X^* > 0$ whenever $\frac{k_h(a\varphi_{P_x} - d_x)}{(a-d_x)} > \left(1 + \frac{c\varphi_{P_z}}{d_z}\right)\frac{(b_1\varphi_{P_{y_1}}g\frac{c\varphi_{P_z}}{d_z} - (g\alpha - d_1))}{(b_1 - d_1)\frac{(1+c\varphi_{P_z})}{d_z k_t}}$. Hence the following results.

Theorem 2.2. *When $\min\left(1, g \frac{Z-\alpha Y_1}{Y_1}\right) \neq 1$ and the following conditions hold.*

- (i) $a > d_x$,
- (ii) $b_1 > d_1$,
- (ii) $b_1\varphi_{P_{y_1}}g\frac{c\varphi_{P_z}}{d_z} > (g\alpha - d_1)$,
- (iv) $\frac{k_h(a\varphi_{P_x} - d_x)}{(a-d_x)} > \left(1 + \frac{c\varphi_{P_z}}{d_z}\right)\frac{(b_1\varphi_{P_{y_1}}g\frac{c\varphi_{P_z}}{d_z} - (g\alpha - d_1))}{(b_1 - d_1)\frac{(1+c\varphi_{P_z})}{d_z k_t}}$,

then the homogeneous tumor growth model has a unique positive constant solution

$$(X^*, Y_1^*, Z^*) = \begin{pmatrix} \frac{k_h(a\varphi_{P_x} - d_x)}{(a-d_x)} - \left(1 + \frac{c\varphi_{P_z}}{d_z}\right)\frac{(b_1\varphi_{P_{y_1}}g\frac{c\varphi_{P_z}}{d_z} - (g\alpha - d_1))}{(b_1 - d_1)\frac{(1+c\varphi_{P_z})}{d_z k_t}} \\ \frac{(b_1\varphi_{P_{y_1}}g\frac{c\varphi_{P_z}}{d_z} - (g\alpha - d_1))}{(b_1 - d_1)\frac{(1+c\varphi_{P_z})}{d_z k_t}} \\ \frac{c\varphi_{P_z}}{d_z}Y_1^* \end{pmatrix}. \quad (16)$$

Similarly, when the maximum proliferation rate of tumor cells drops below unity, then the steady states are positive as long as the genetically determined, carrying capacity for healthy cells is bigger than that of the tumour cells.

2.3. **Global stability of the uniform steady states.** In this section we show that the uniform positive steady states are globally uniform. Since the homogeneous

tumour growth model is of quasi-Lotka-Vorterra type [6], we let $V : \mathbb{R}_{\geq 0}^3 \rightarrow \mathbb{R}$ defined by

$$V(X, Y_1, Z) = \left(X - X^* - X^* \log \left(\frac{X}{X^*} \right) \right) + \left(Y_1 - Y_1^* - Y_1^* \log \left(\frac{Y_1}{Y_1^*} \right) \right) + \left(Z - Z^* - Z^* \log \left(\frac{Z}{Z^*} \right) \right),$$

then we see that $V(X^*, Y_1^*, Z^*) = 0$ and $V(X, Y_1, Z) > 0$ for all $(X, Y_1, Z) \neq (X^*, Y_1^*, Z^*)$. Moreover, on $\mathbb{R}_{\geq 0}^3$, we have

$$\begin{aligned} \frac{dV(X, Y_1, Z)}{dt} &= V_x \dot{X} + V_{y_1} \dot{Y}_1 + V_z \dot{Z} \\ &= \left(1 - \frac{X^*}{X} \right) X \left(a\varphi_{P_x} - d_x - (a - d_x) \frac{X + Y_1 + Z}{k_h} \right) \end{aligned} \quad (17)$$

$$+ \left(1 - \frac{Y_1^*}{Y_1} \right) Y_1 \left(b_1 \varphi_{P_{y_1}} \min \left(1, g \frac{Z - \alpha Y_1}{Y_1} \right) - d_1 - (b_1 - d_1) \frac{Y_1 + Z}{k_t} \right) + \left(1 - \frac{Z^*}{Z} \right) c \min \varphi_{P_z} Y_1 - d_z Z,$$

$$\begin{aligned} &= (X - X^*) \left(a\varphi_{P_x} - d_x - (a - d_x) \frac{X + Y_1 + Z}{k_h} \right) \\ &+ (Y_1 - Y_1^*) \left(b_1 \varphi_{P_{y_1}} \min \left(1, g \frac{Z - \alpha Y_1}{Y_1} \right) - d_1 - (b_1 - d_1) \frac{Y_1 + Z}{k_t} \right) \\ &+ (Z - Z^*) (c\varphi_{P_z} Y_1 - d_z (Z - Z^*)), \end{aligned} \quad (18)$$

upon multiplying the last equation with Z . When $\min \left(1, g \frac{Z - \alpha Y_1}{Y_1} \right) \equiv 1$, then equation in (17) becomes

$$\begin{aligned} \frac{dV(X, Y_1, Z)}{dt} &= (X - X^*) \left(- (a - d_x) \frac{(X - X^*) + (Y_1 - Y_1^*) + (Z - Z^*)}{k_h} \right) \\ &+ (Y_1 - Y_1^*) \left(- (b_1 - d_1) \frac{(Y_1 - Y_1^*) + (Z - Z^*)}{k_t} \right) \\ &+ (Z - Z^*) (c\varphi_{P_z} (Y_1 - Y_1^*) - d_z (Z - Z^*)). \end{aligned} \quad (19)$$

Let $\bar{X} = X - X^*$, $\bar{Y}_1 = Y_1 - Y_1^*$, $\bar{Z} = Z - Z^*$, then the equation in (19) becomes

$$\begin{aligned} \frac{dV(X, Y_1, Z)}{dt} &= - (a - d_x) X \left(\frac{X + Y_1 + Z}{k_h} \right) \\ &- (b_1 - d_1) Y_1 \left(\frac{Y_1 + Z}{k_t} \right) + Z (c\varphi_{P_z} Y - d_z Z) \leq 0, \end{aligned} \quad (20)$$

after dropping the bar signs. Similarly, $\min \left(1, g \frac{Z - \alpha Y_1}{Y_1} \right) \neq 1$, then equation in (17) becomes

$$\begin{aligned} \frac{dV(X, Y_1, Z)}{dt} &= - (a - d_x) (X - X^*) \left(\frac{X + Y_1 + Z}{k_h} \right) \\ &- \frac{(b_1 - d_1)}{k_t} (Y_1 - Y_1^*) \left((Y_1 - Y_1^*) + (b_1 \varphi_{P_{y_1}} g - 1)(Z - Z^*) \right) \\ &+ (Z - Z^*) (c\varphi_{P_z} Y_1 - d_z (Z - Z^*)) \leq 0. \end{aligned} \quad (21)$$

Thus, we have the following results.

Theorem 2.3. *The positive steady states in equation (12) and (16) are globally stable.*

Thus, in this section we determine the positive solutions of both cases and found out that similar conditions hold for the survival of tumour cells which play an integral part in this stoichometric dynamics.

In the next sections we consider the existence of Hopf bifurcation.

2.4. Stability of uniform equilibrium points and the existence of Hopf bifurcation for $\min\left(1, g\frac{Z-\alpha Y_1}{Y_1}\right) = 1$ and $\min\left(1, g\frac{Z-\alpha Y_1}{Y_1}\right) \neq 1$. In this section, we concentrate on the dynamical behavior of equation (2). Our goal is to investigate the stability of the equilibrium points of (2) and also the existence of Hopf bifurcation. This is achieved by taking the delay time τ as a bifurcation parameter. Thus, we study effects of the time delay on the dynamics of (2) as follows.

2.4.1. Stability of positive equilibrium points and the existence of Hopf bifurcation for $\min\left(1, g\frac{Z-\alpha Y_1}{Y_1}\right) = 1$. Let (X^*, Y_1^*, Z^*) be an equilibrium point for the system in equation (2) and

$$(\bar{X}, \bar{Y}_1, \bar{Z}) = (X - X^*, Y_1 - Y_1^*, Z - Z^*).$$

Linearizing the system in equation (2) around (X^*, Y_1^*, Z^*) , and drop bars again, we obtain

$$\left. \begin{aligned} X_t - \mathcal{D}_x \Delta X &= \left(a\varphi_{P_x} - d_x - (a - d_x) \frac{2X^* + Y_1^* + Z^*}{k_h} \right) X - (a - d_x) \frac{X^*}{k_h} Y_1 \\ &\quad - (a - d_x) \frac{X^*}{k_h} Z, \\ (Y_1)_t - \mathcal{D}_{y_1} \Delta Y_1 &= \left(\varphi_{P_{y_1}} - d_1 - (b_1 - d_1) \frac{2Y_1^* + Z^*}{k_t} \right) Y_1 - \frac{Y_1^* (b_1 - d_1)}{k_t} Z, \\ Z_t - \mathcal{D}_z \Delta Z &= c\varphi_{P_z} Y_1(t - \tau) - d_z Z, \\ \frac{\partial X}{\partial \nu} = \frac{\partial Y_1}{\partial \nu} = \frac{\partial Y_2}{\partial \nu} = \frac{\partial Z}{\partial \nu} &= 0, \text{ on } (x, t) \in \partial\Omega \times (0, \infty), \\ \mathcal{X}_j(x, t) &= \eta_j(x, t) \geq 0(x, t) \in \Omega \times (0, \infty), \\ \mathcal{X}_j(x, t) &= \eta_j(x, t) - \mathcal{X}_j^*, (x, t) \in \bar{\Omega} \times [-\tau, 0], j = 1, 2, 3. \end{aligned} \right\} \quad (22)$$

Let $0 = \mu_0 < \mu_1 < \dots$ be the eigenvalues of the operator Δ on Ω with the homogeneous Neumann boundary condition, then the characteristic equation for equation in (22) is given by

$$\left. \begin{aligned} \lambda + \mathcal{D}_x \mu_k + a\varphi_{P_x} - d_x - \frac{(a-d_x)}{k_h} (2X^* + Y_1^* + Z^*) &= 0, \\ \lambda^2 k_t + \mathcal{K}_1 \lambda + Y_1^* c (b_1 - d_1) \varsigma_{P_z} \exp(-\lambda\tau) + \mathcal{K}_2 &= 0, \end{aligned} \right\} \quad (23)$$

where

$$\begin{aligned} \mathcal{K}_1 &= k_t (\mathcal{D}_z + \mathcal{D}_{y_1}) \mu_k + (\varphi_{P_{y_1}} - (d_1 + d_z)) k_t - (2Y_1^* + Z^*) (d_1 - b_1), \\ \mathcal{K}_2 &= \mathcal{D}_{y_1} \mathcal{D}_z k_t \mu_k^2 + k_t (\varphi_{P_{y_1}} \mathcal{D}_z - \mathcal{D}_{y_1} d_z) \mu_k + \mathcal{D}_z ((d_1 - b_1) (2Y_1^* + Z^*) - d_1 k_t) \mu_k \\ &\quad + d_z (2Y_1^* + Z^*) (b_1 - d_1) + k_t (d_1 - \varphi_{P_{y_1}}) d_z. \end{aligned}$$

Negative real parts for the first equation in (23) requires that

$$k_h d_x > -(a - d_x), \quad (24)$$

whereas in the second equation in (23), when $\tau = 0$, Routh-Hurwitz criteria requires that

$$(\varphi_{P_{y_1}} - (d_1 + d_z))k_t > (2Y_1^* + Z^*)(d_1 - b_1), \quad \varphi_{P_{y_1}} \mathcal{D}_z > \mathcal{D}_{y_1} d_z, \quad d_1 > \varphi_{P_{y_1}}. \quad (25)$$

Therefore, we have the following result.

Lemma 2.4. *Assume that the conditions in equation (24)-(25) holds. Then the positive constant solution (X^*, Y_1^*, Z^*) of system in (2) is locally asymptotically stable when $\tau = 0$.*

Next, we examine when equation in (23) has pure imaginary roots $\lambda = \pm i\omega$ with ω real number and $\omega > 0$. This is given by the following lemma.

Lemma 2.5. *The characteristic equation associated to equation in (23) has pure imaginary roots.*

Proof. If $\lambda = i\omega$ be a root of the characteristic equation (23) where $\omega > 0$, then we have

$$-\omega^2 k_t + \mathcal{K}_1 i\omega + Y_1^* c(b_1 - d_1) \varsigma_{P_z} (\cos(\omega\tau) + i \sin(\omega\tau)) + \mathcal{K}_2 = 0. \quad (26)$$

Separating real and imaginary parts, we have the following two equations

$$\begin{aligned} -\omega^2 k_t + Y_1^* c(b_1 - d_1) \varsigma_{P_z} \cos(\omega\tau) + \mathcal{K}_2 &= 0, \\ \mathcal{K}_1 \omega + Y_1^* c(b_1 - d_1) \varsigma_{P_z} \sin(\omega\tau) &= 0. \end{aligned} \quad (27)$$

Equations in (27) give possible values of τ and ω for which the characteristic equation in (23) can have pure imaginary roots. To see it we square each equation and we obtain

$$\begin{aligned} (Y_1^* c(b_1 - d_1) \varsigma_{P_z})^2 \cos^2(\omega\tau) &= (\omega^2 k_t - \mathcal{K}_2)^2, \\ (Y_1^* c(b_1 - d_1) \varsigma_{P_z})^2 \sin^2(\omega\tau) &= (\mathcal{K}_1 \omega)^2. \end{aligned} \quad (28)$$

Adding the two equations, we obtain

$$2(Y_1^* c(b_1 - d_1) \varsigma_{P_z})^2 = (\omega^2 k_t - \mathcal{K}_2)^2 + (\mathcal{K}_1 \omega)^2, \quad (29)$$

which implies that

$$\omega^4 + \frac{(\mathcal{K}_1^2 - 2k_t \mathcal{K}_2)}{k_t} \omega^2 + \frac{\mathcal{K}_2^2 - 2(Y_1^* c(b_1 - d_1) \varsigma_{P_z})^2}{k_t} = 0. \quad (30)$$

Hence,

$$\omega^2 = \frac{-\frac{(\mathcal{K}_1^2 - 2k_t \mathcal{K}_2)}{k_t} \pm \sqrt{\left(\frac{(\mathcal{K}_1^2 - 2k_t \mathcal{K}_2)}{k_t}\right)^2 - 4 \frac{\mathcal{K}_2^2 - 2(Y_1^* c(b_1 - d_1) \varsigma_{P_z})^2}{k_t}}}{2} \quad (31)$$

Thus, in view of the first equation in (27) and the first equation in (28), we obtain

$$\tau_j^* = \frac{1}{\omega} \cos^{-1} \left(\left(\frac{(\omega^2 k_t - \mathcal{K}_2)}{Y_1^* c(b_1 - d_1) \varsigma_{P_z}} \right) + 2j\pi \right), \quad (32)$$

as the critical values of τ , for $j = 0, 1, 2, \dots$, and this complete the proves. This gives us the following lemma. \square

Lemma 2.6. *Assume that the conditions in equation (24) and (25) hold. Then for $j \in \mathbb{N}_0$ the following statements are true.*

- (i) *Equation in (28) has a pair of purely imaginary roots $\pm i\omega$ when $\tau = \tau_j^*$ and there are no other roots of equation in (28) with zero real parts.*

(ii) All the roots of equation in (28) have negative real parts when $\tau \in [0, \tau^*)$, where $\tau^* = \tau_0^*$.

We have verified the hypotheses for Hopf bifurcation to occur at $\tau^* = \tau_0^*$ except for the transversality condition. Differentiate the second equation in (23) with respect to τ , we have

$$\operatorname{Re} \left(\frac{\partial \lambda_2^2 k_t + \mathcal{K}_1 \lambda_2 + Y_1^* c (b_1 - d_1) \varsigma_{P_z} \exp(-\lambda_2 \tau) + \mathcal{K}_2}{\partial \tau} \right) \Big|_{\lambda=i\omega, \tau=\tau_0^*} \quad (33)$$

$$= \operatorname{Re} (\omega Y_1^* c (b_1 - d_1) \varsigma_{P_z} \sin(\omega \tau_0^*)) > 0. \quad (34)$$

Thus, the following results.

Lemma 2.7. *The transversality condition*

$$\operatorname{Re} \left(\frac{\partial \lambda_2^2 k_t + \mathcal{K}_1 \lambda_2 + Y_1^* c (b_1 - d_1) \varsigma_{P_z} \exp(-\lambda_2 \tau) + \mathcal{K}_2}{\partial \tau} \right) \Big|_{\lambda=i\omega, \tau=\tau_0^*} > 0,$$

is satisfied.

2.4.2. *Stability of positive equilibrium points and the existence of Hopf bifurcation* for $\min \left(1, g \frac{Z - \alpha Y_1}{Y_1} \right) \neq 1$. Similarly, after linearizing the system in equation (2) around (X^*, Y_1^*, Z^*) , we obtain the characteristic equation as

$$\left. \begin{aligned} \lambda + \mathcal{D}_x \mu_k + a \varphi_{P_x} - d_x - \frac{(a-d_x)}{k_h} (2X^* + Y^* + Z^*) &= 0, \\ \lambda^2 k_t + \mathcal{K}_1 \lambda + c \mathcal{D}_z (b_1 - d_1) Y_1^* \exp(-\lambda \tau) + \mathcal{K}_2 &= 0, \end{aligned} \right\} \quad (35)$$

where

$$\begin{aligned} \mathcal{K}_1 &= (\varphi_{P_{y_1}} - d_z - d_1) k_t + (d_1 - b_1) (Z^* + 2Y_1^*) + k_t (\mathcal{D}_{y_1} + \mathcal{D}_z) \mu_k, \\ \mathcal{K}_2 &= d_z ((d_1 - \varphi_{P_{y_1}}) k_t + (b_1 - d_1) (2Y_1^* + Z^*)) + k_t \mathcal{D}_{y_1} \mu_k^2 \mathcal{D}_z \\ &\quad + k_t (\varphi_{P_{y_1}} \mathcal{D}_z - \mathcal{D}_{Y_1} d_z - d_1 \mathcal{D}_z) \mu_k + \mathcal{D}_z (d_1 - b_1) (2Y_1^* + Z^*) \mu_k. \end{aligned}$$

Negative real parts for the first equation in (35) requires that

$$k_h d_x > -(a - d_x), \quad (36)$$

whereas in the second equation in (35), when $\tau = 0$, Routh-Hurwitz criteria requires that

$$(\varphi_{P_{y_1}} - (d_1 + d_z)) k_t > (2Y_1^* + Z^*) (d_1 - b_1), \quad \varphi_{P_{y_1}} \mathcal{D}_z > \mathcal{D}_{y_1} d_z + d_1 \mathcal{D}_z, \quad d_1 > \varphi_{P_{y_1}}. \quad (37)$$

Therefore, we have the following result.

Lemma 2.8. *Assume that the conditions in equation (36)-(37) holds. Then the positive constant solution (X^*, Y_1^*, Z^*) of system (2) is locally asymptotically stable when $\tau = 0$.*

Next, we examine when equation in (35) has pure imaginary roots $\lambda = \pm i\omega$ with ω real number and $\omega > 0$. This is given by the following lemma.

Lemma 2.9. *The characteristic equation associated to equation in (35) has pure imaginary roots.*

Proof. If $\lambda = i\omega$ be a root of the characteristic equation (35) where $\omega > 0$, then we have

$$-\omega^2 k_t + \mathcal{K}_1 i\omega + Y_1^* c (b_1 - d_1) \mathcal{D}_z (\cos(\omega \tau) + i \sin(\omega \tau)) + \mathcal{K}_2 = 0. \quad (38)$$

Separating real and imaginary parts, we have the following two equations

$$\begin{aligned} -\omega^2 k_t + Y_1^* c(b_1 - d_1) \mathcal{D}_z \cos(\omega\tau) + \mathcal{K}_2 &= 0, \\ \mathcal{K}_1 \omega + Y_1^* c(b_1 - d_1) \mathcal{D}_z \sin(\omega\tau) &= 0. \end{aligned} \tag{39}$$

Equations in (39) give possible values of τ and ω for which the characteristic equation in (35) can have pure imaginary roots. To see it we square each equation and we obtain

$$\begin{aligned} (Y_1^* c(b_1 - d_1) \mathcal{D}_z)^2 \cos^2(\omega\tau) &= (\omega^2 k_t - \mathcal{K}_2)^2, \\ (Y_1^* c(b_1 - d_1) \mathcal{D}_z)^2 \sin^2(\omega\tau) &= (\mathcal{K}_1 \omega)^2. \end{aligned} \tag{40}$$

Adding the two equations, we obtain

$$2(Y_1^* c(b_1 - d_1) \mathcal{D}_z)^2 = (\omega^2 k_t - \mathcal{K}_2)^2 + (\mathcal{K}_1 \omega)^2, \tag{41}$$

which implies that

$$\omega^4 + \frac{(\mathcal{K}_1^2 - 2k_t \mathcal{K}_2)}{k_t} \omega^2 + \frac{\mathcal{K}_2^2 - 2(Y_1^* c(b_1 - d_1) \mathcal{D}_z)^2}{k_t} = 0. \tag{42}$$

Hence,

$$\omega^2 = \frac{-\frac{(\mathcal{K}_1^2 - 2k_t \mathcal{K}_2)}{k_t} \pm \sqrt{\left(\frac{(\mathcal{K}_1^2 - 2k_t \mathcal{K}_2)}{k_t}\right)^2 - 4\frac{\mathcal{K}_2^2 - 2(Y_1^* c(b_1 - d_1) \mathcal{D}_z)^2}{k_t}}}{2} \tag{43}$$

Thus, in view of the first equation in (40) and equation in (43), we obtain

$$\tau_j^* = \frac{1}{\omega} \cos^{-1} \left(\left(\frac{(\omega^2 k_t - \mathcal{K}_2)}{Y_1^* c(b_1 - d_1) \mathcal{D}_z} \right) + 2j\pi \right), \tag{44}$$

are the critical values of τ , for $j = 0, 1, 2, \dots$, and this complete the proves. This gives us the following lemma. □

Lemma 2.10. *Assume that the conditions in equation (36) and (37) hold. Then for $j \in \mathbb{N}_0$ the following statements are true.*

- (i) *Equation in (35) has a pair of purely imaginary roots $\pm i\omega$ when $\tau = \tau_j^*$ and there are no other roots of equation in (35) with zero real parts.*
- (ii) *All the roots of equation in (35) have negative real parts when $\tau \in [0, \tau^*)$, where $\tau^* = \tau_0^*$.*

We have verified the hypotheses for Hopf bifurcation to occur at $\tau^* = \tau_0^*$ except for the transversality condition. Differentiate the second equation in (35) with respect to τ , we have

$$\operatorname{Re} \left(\frac{\partial \lambda_2^2 k_t + \mathcal{K}_1 \lambda_2 + Y_1^* c(b_1 - d_1) \mathcal{D}_z \exp(-\lambda_2 \tau) + \mathcal{K}_2}{\partial \tau} \right) \Big|_{\lambda=i\omega, \tau=\tau_0^*} \tag{45}$$

$$= \operatorname{Re} (\omega Y_1^* c(b_1 - d_1) \mathcal{D}_z \sin(\omega\tau_0^*)) > 0. \tag{46}$$

Thus, the following results.

Lemma 2.11. *The transversality condition*

$$\operatorname{Re} \left(\frac{\partial \lambda_2^2 k_t + \mathcal{K}_1 \lambda_2 + Y_1^* c(b_1 - d_1) \varsigma_{P_z} \exp(-\lambda_2 \tau) + \mathcal{K}_2}{\partial \tau} \right) \Big|_{\lambda=i\omega, \tau=\tau_0^*} > 0,$$

is satisfied.

In the next section we derive our efficient numerical method.

3. Derivation of the numerical method. In this section, we describe the derivation of the fitted numerical method for solving the system in equation (2). We determine an approximation to the derivatives of the functions $X(t, x)$, $Y_1(x, t)$ and $Z(t, x)$ with respect to the spatial variable x .

Let N_x be a positive integer. Discretize the interval $[0, x_f]$ through the points

$$0 = x_0 < x_1 < x_2 < \cdots < x_{N_x} = x_f,$$

where the step-size $\Delta x = x_{j+1} - x_j = x_f/N_x$, $j = 0, 1, \dots, N_x$. Let $\mathcal{X}_j(t)$, $(\mathcal{Y}_1)_j(t)$, $\mathcal{Z}_j(t)$ denote the numerical approximations of $X(t, j)$, $Y_1(t, j)$, $Z(t, j)$, then we approximate the second order spatial derivatives by

$$\begin{aligned} \Delta X(t, x_j) &\approx \frac{\mathcal{X}_{j+1} - 2\mathcal{X}_j + \mathcal{X}_{j-1}}{(\phi_X)^2}, \quad \Delta Y_1(t, x_j) \approx \frac{(\mathcal{Y}_1)_{j+1} - 2(\mathcal{Y}_1)_j + (\mathcal{Y}_1)_{j-1}}{(\phi_{Y_1})^2}, \\ \Delta Z(t, x_j) &\approx \frac{\mathcal{Z}_{j+1} - 2\mathcal{Z}_j + \mathcal{Z}_{j-1}}{(\phi_Z)^2}, \end{aligned} \quad (47)$$

where

$$\begin{aligned} (\phi_X)^2 &= \frac{4}{(\sigma_X)^2} \sin^2 \left(\frac{(\sigma_X)_j \Delta x}{4} \right), \quad (\phi_{Y_1})^2 = \frac{(1 - \exp((\sigma_{Y_1}) \Delta x))}{(\sigma_{Y_1})^2}, \\ (\phi_Z)^2 &= \frac{(1 - \exp((\sigma_Z) \Delta x))}{(\sigma_Z)^2}, \end{aligned}$$

and

$$(\sigma_X) = \sqrt{\frac{(d_x - a\varphi_{P_x})}{\mathcal{D}_x}}, \quad (\sigma_{Y_1}) = \sqrt{\frac{d_1}{\mathcal{D}_{y_1}}}, \quad (\sigma_Z) = \sqrt{\frac{d_z}{\mathcal{D}_z}}. \quad (48)$$

It is obvious that all the $\phi \rightarrow \Delta x$ as $\Delta x \rightarrow 0$.

Let N_t be a positive integer and $\Delta t = T/N_t$ where $0 < t < T$. Discretizing the time interval $[0, T]$ through the points

$$0 = t_0 < t_1 < \cdots < t_{N_t} = T,$$

where

$$t_{n+1} - t_n = \Delta t, \quad n = 0, 1, \dots, (N_t - 1).$$

We approximate the time derivatives at t_n by

$$\frac{d\mathcal{X}_j(t_n)}{dt} \approx \frac{\mathcal{X}_j^{n+1} - \mathcal{X}_j^n}{\psi_X}, \quad \frac{d(\mathcal{Y}_1)_j(t_n)}{dt} \approx \frac{(\mathcal{Y}_1)_j^{n+1} - (\mathcal{Y}_1)_j^n}{\psi_{Y_1}}, \quad \frac{d\mathcal{Z}_j(t_n)}{dt} \approx \frac{\mathcal{Z}_j^{n+1} - \mathcal{Z}_j^n}{\psi_Z}, \quad (49)$$

where

$$\begin{aligned} \psi_X &= (\exp((d_x - a\varphi_{P_x})\Delta t) - 1)/(d_x - a\varphi_{P_x}), \quad \psi_{Y_1} = (1 - \exp(-d_1\Delta t))/d_1, \\ \psi_Z &= (1 - \exp(-d_z\Delta t))/d_z, \end{aligned} \quad (50)$$

where we see that all the $\psi \rightarrow \Delta t$ as $\Delta t \rightarrow 0$.

The denominator functions in (47) and (49) are used explicitly to remove the inherent stiffness in the central finite derivatives parts and are derived by using the theory of nonstandard finite difference methods, see, e.g., [9, 16, 17] and references therein.

Combining the equation (47) for the spatial derivatives with equation (49) for time derivatives, we obtain

$$\left. \begin{aligned}
 \frac{\mathcal{X}_j^{n+1} - \mathcal{X}_j^n}{\psi_X} &= \mathcal{D}_x \frac{\mathcal{X}_{j+1}^{n+1} - 2\mathcal{X}_j^{n+1} + \mathcal{X}_{j-1}^{n+1}}{(\phi_X)^2} \\
 &\quad + \mathcal{X}_j^n \left(a\varphi_{P_x} - d_x - (a - d_x) \frac{\mathcal{X}_j^n + (\mathcal{Y}_1)_j^n + \mathcal{Z}_j^n}{k_h} \right), \\
 \frac{(\mathcal{Y}_1)_j^{n+1} - (\mathcal{Y}_1)_j^n}{\psi_{Y_1}} &= \mathcal{D}_{y_1} \frac{(\mathcal{Y}_1)_{j+1}^{n+1} - 2(\mathcal{Y}_1)_j^{n+1} + (\mathcal{Y}_1)_{j-1}^{n+1}}{(\phi_{Y_1})^2} \\
 &\quad + (\mathcal{Y}_1)_1^n \left(b_1\varphi_{P_{y_1}} \min \left(1, g \frac{\mathcal{Z}_j^n - \alpha(\mathcal{Y}_1)_j^n}{(\mathcal{Y}_1)_j^n} \right) - d_1 - (b_1 - d_1) \frac{(\mathcal{Y}_1)_j^n + \mathcal{Z}_j^n}{k_t} \right), \\
 \frac{\mathcal{Z}_j^{n+1} - \mathcal{Z}_j^n}{\psi_Z} &= \mathcal{D}_z \frac{\mathcal{Z}_{j+1}^{n+1} - 2\mathcal{Z}_j^{n+1} + \mathcal{Z}_{j-1}^{n+1}}{(\phi_Z)^2} + c\varphi_{P_z} (\mathcal{H}_{Y_1})_j^n - d_z \mathcal{Z}_j^n, \\
 \mathcal{X}_1^n &= \mathcal{X}_{-1}^n, \quad (\mathcal{Y}_1)_1^n = (\mathcal{Y}_1)_{-1}^n, \quad \mathcal{Z}_1^n = \mathcal{Z}_{-1}^n \\
 \mathcal{X}_{N_x}^n &= \mathcal{X}_{N_x-1}^n, \quad (\mathcal{Y}_1)_{N_x}^n = (\mathcal{Y}_1)_{N_x-1}^n, \quad \mathcal{Z}_{N_x}^n = \mathcal{Z}_{N_x-1}^n, \\
 \mathcal{X}_j^0 &= 9.00, \quad (\mathcal{Y}_1)_j^0 = 0.01, \quad \mathcal{Z}_j^0 = 0.001,
 \end{aligned} \right\} \quad (51)$$

where, the no-flux boundary conditions are discretised by means of the central finite difference [2], $j = 1, 2, \dots, N_x - 1$, $n = 0, 1, \dots, N_t - 1$ and

$$(\mathcal{H}_{Y_1})_j^n \approx Y_1(t_n - \tau, x_j), \quad (52)$$

is denoting the history functions corresponding to the equation in Y_1 .

The system in equation (51) can further be simplified as

$$\left. \begin{aligned}
 -\frac{\mathcal{D}_x}{(\phi_X)^2} \mathcal{X}_{j-1}^{n+1} + \left(\frac{1}{\psi_X} + \frac{2\mathcal{D}_x}{(\phi_X)^2} \right) \mathcal{X}_j^{n+1} - \frac{\mathcal{D}_x}{(\phi_X)^2} \mathcal{X}_{j+1}^{n+1} \\
 = \mathcal{X}_j^n \left(\frac{1}{\psi_X} + a\varphi_{P_x} - d_x - (a - d_x) \frac{\mathcal{X}_j^n + (\mathcal{Y}_1)_j^n + \mathcal{Z}_j^n}{k_h} \right), \\
 -\frac{\mathcal{D}_{y_1}}{(\phi_{Y_1})^2} (\mathcal{Y}_1)_{j-1}^{n+1} + \left(\frac{1}{\psi_{Y_1}} + \frac{2\mathcal{D}_{y_1}}{(\phi_{Y_1})^2} \right) (\mathcal{Y}_1)_j^{n+1} - \frac{\mathcal{D}_{y_1}}{(\phi_{Y_1})^2} (\mathcal{Y}_1)_{j+1}^{n+1} \\
 = (\mathcal{Y}_1)_1^n \left(\frac{1}{\psi_{Y_1}} + b_1\varphi_{P_{y_1}} \min \left(1, g \frac{\mathcal{Z}_j^n - \alpha(\mathcal{Y}_1)_j^n}{(\mathcal{Y}_1)_j^n} \right) - d_1 - (b_1 - d_1) \frac{(\mathcal{Y}_1)_j^n + \mathcal{Z}_j^n}{k_t} \right), \\
 -\frac{\mathcal{D}_z}{(\phi_Z)^2} \mathcal{Z}_{j-1}^{n+1} + \left(\frac{1}{\psi_Z} + \frac{2\mathcal{D}_z}{(\phi_Z)^2} \right) \mathcal{Z}_j^{n+1} - \frac{\mathcal{D}_z}{(\phi_Z)^2} \mathcal{Z}_{j+1}^{n+1} \\
 = c\varphi_{P_z} (\mathcal{H}_{Y_1})_j^n + \left(\frac{1}{\psi_Z} - d_z \right) \mathcal{Z}_j^n,
 \end{aligned} \right\} \quad (53)$$

which can be written as a tridiagonal system given by

$$\left. \begin{aligned}
 \mathcal{P}_X^{n+1} &= \mathcal{X}_j^n \left(\frac{1}{\psi_X} + a\varphi_{P_x} - d_x - (a - d_x) \frac{\mathcal{X}_j^n + (\mathcal{Y}_1)_j^n + \mathcal{Z}_j^n}{k_h} \right), \\
 \mathcal{P}_{Y_1}^{n+1} &= (\mathcal{Y}_1)_1^n \left(\frac{1}{\psi_{Y_1}} + b_1\varphi_{P_{y_1}} \min \left(1, g \frac{\mathcal{Z}_j^n - \alpha(\mathcal{Y}_1)_j^n}{(\mathcal{Y}_1)_j^n} \right) - d_1 \right. \\
 &\quad \left. - (b_1 - d_1) \frac{(\mathcal{Y}_1)_j^n + \mathcal{Z}_j^n}{k_t} \right), \\
 \mathcal{P}_Z^{n+1} &= c\varphi_{P_z} (\mathcal{H}_{Y_1})_j^n + \left(\frac{1}{\psi_Z} - d_z \right) \mathcal{Z}_j^n,
 \end{aligned} \right\} \quad (54)$$

where $j = 1, \dots, N_x - 1$, $n = 0, \dots, N_t - 1$ and

$$\left. \begin{aligned} \mathcal{P}_E^{n+1} &= \text{Tri} \left(-\frac{\mathcal{D}_x}{(\phi_x)^2}, \frac{1}{\psi_x} + \frac{2\mathcal{D}_x}{(\phi_x)^2}, -\frac{\mathcal{D}_x}{(\phi_x)^2} \right), \\ \mathcal{P}_{Y_1}^{n+1} &= \text{Tri} \left(-\frac{\mathcal{D}_{y_1}}{(\phi_{Y_1})^2}, \frac{1}{\psi_{Y_1}} + \frac{2\mathcal{D}_{y_1}}{(\phi_{Y_1})^2}, -\frac{\mathcal{D}_{y_1}}{(\phi_{Y_1})^2} \right), \\ \mathcal{P}_Z^{n+1} &= \text{Tri} \left(-\frac{\mathcal{D}_z}{(\phi_z)^2}, \frac{1}{\psi_z} + \frac{2\mathcal{D}_z}{(\phi_z)^2}, -\frac{\mathcal{D}_z}{(\phi_z)^2} \right). \end{aligned} \right\}$$

On the interval $[0, \tau]$ the delayed arguments $t_n - \tau$ belong to $[-\tau, 0]$, and therefore the delayed variables in equation (51) are evaluated directly from the history functions $Y_1^0(t, x)$ as

$$(\mathcal{H}_{Y_1})_j^n \approx Y_1^0(t_n - \tau, x_j), \quad (55)$$

and equation (54) becomes

$$\left. \begin{aligned} \mathcal{P}_X^{n+1} &= \mathcal{X}_j^n \left(\frac{1}{\psi_x} + a\varphi_{P_x} - d_x - (a - d_x) \frac{\mathcal{X}_j^n + (\mathcal{Y}_1)_j^n + \mathcal{Z}_j^n}{k_h} \right), \\ \mathcal{P}_{Y_1}^{n+1} &= (\mathcal{Y}_1)_1^n \left(\frac{1}{\psi_{Y_1}} + b_1\varphi_{P_{Y_1}} \min \left(1, g \frac{\mathcal{Z}_j^n - \alpha(\mathcal{Y}_1)_j^n}{\mathcal{Y}_1)_j^n} \right) - d_1 \right. \\ &\quad \left. - (b_1 - d_1) \frac{(\mathcal{Y}_1)_j^n + \mathcal{Z}_j^n}{k_t} \right), \\ \mathcal{P}_Z^{n+1} &= c\varphi_{P_z} (\mathcal{Y})_1^0(t_n - \tau, x_j) + \left(\frac{1}{\psi_z} - d_z \right) \mathcal{Z}_j^n. \end{aligned} \right\} \quad (56)$$

Let s be the largest integer such that $\tau_s \leq \tau$. By using the system equation (56) we can compute $\mathcal{X}_j^n, (\mathcal{Y}_1)_j^n, \mathcal{Z}_j^n$ for $1 \leq n \leq s$. Up to this stage, we interpolate the data

$$(t_0, (\mathcal{Y}_1)_j^0), (t_1, (\mathcal{Y}_1)_j^1), \dots, (t_s, (\mathcal{Y}_1)_j^s),$$

using an interpolating cubic Hermite spline $\iota_j(t)$. Then

$$(\mathcal{Y}_1)_j^n = \iota_{Y_1}(t_n, x_j),$$

for all $n = 0, 1, \dots, s$ and $j = 1, 2, \dots, N_x - 1$.

For $n = s + 1, s + 2, \dots, N_t - 1$, when we move from level n to level $n + 1$ we extend the definitions of the cubic Hermite spline $\iota_j(t)$ to the point $(t_n + k, (\mathcal{Y}_1)_j^n)$. Then the history term $(\mathcal{H}_{Y_1})_j^n$ can be approximated by the functions $\iota_j(t_n - \tau)$ for $n \geq s$. This implies that,

$$(\mathcal{H}_{Y_1})_j^n \approx (\iota_{Y_1})_j(t_n - \tau), \quad (57)$$

and equation (56) becomes

$$\left. \begin{aligned} \mathcal{P}_X^{n+1} &= \mathcal{X}_j^n \left(\frac{1}{\psi_x} + a\varphi_{P_x} - d_x - (a - d_x) \frac{\mathcal{X}_j^n + (\mathcal{Y}_1)_j^n + \mathcal{Z}_j^n}{k_h} \right), \\ \mathcal{P}_{Y_1}^{n+1} &= (\mathcal{Y}_1)_1^n \left(\frac{1}{\psi_{Y_1}} + b_1\varphi_{P_{Y_1}} \min \left(1, g \frac{\mathcal{Z}_j^n - \alpha(\mathcal{Y}_1)_j^n}{\mathcal{Y}_1)_j^n} \right) - d_1 \right. \\ &\quad \left. - (b_1 - d_1) \frac{(\mathcal{Y}_1)_j^n + \mathcal{Z}_j^n}{k_t} \right), \\ \mathcal{P}_Z^{n+1} &= c\varphi_{P_z} (\iota_{Y_1})_j(t_n - \tau) + \left(\frac{1}{\psi_z} - d_z \right) \mathcal{Z}_j^n, \end{aligned} \right\} \quad (58)$$

where

$$\iota_{Y_1}(t_n - \tau) = [(\mathcal{H}_{Y_1})_1^n, (\mathcal{H}_{Y_1})_2^n \dots, (\mathcal{H}_{Y_1})_{N_x-1}^n]'$$

Our FOFDM is then consists of equations (51)-(58). This method is analyzed for convergence in next section and the corresponding numerical results are presented in Section 4.

3.1. Analysis of convergence. The convergence for the proposed FOFDM is proved via consistency and stability.

3.1.1. Consistency of the numerical method. We assume that the functions $X(t, x)$, $Y_1(t, x)$, $Z(t, x)$ and their partial derivatives with respect to both t and x are smooth and satisfy

$$\left| \frac{\partial^{i+j} X(t, x)}{\partial t^i x^j} \right| \leq C_X, \quad \left| \frac{\partial^{i+j} Y_1(t, x)}{\partial t^i x^j} \right| \leq C_{Y_1}, \quad \left| \frac{\partial^{i+j} Z(t, x)}{\partial t^i x^j} \right| \leq C_Z, \quad \forall i, j \geq 0, \quad (59)$$

where C_X, C_{Y_1}, C_Z are constant that are independent of the time and space step-sizes.

The local truncation error (LTE) for the discrete equations in X, Y_1, Z in the FOFDM (56) and (58) is given by

$$\left. \begin{aligned} \text{(LTE)}_X &= \left(X_t - \frac{X_j^{n+1} - X_j^n}{\psi_x} \right) - \left(X_{xx} - \frac{X_{j+1}^{n+1} - 2X_j^{n+1} + X_{j-1}^{n+1}}{(\phi_x)_j^2} \right) \\ &\quad + (f_1(t, x, X, Y_1, Z) - f_1(t, x, X_j^n, (Y_1)_j^n, Z_j^n)), \\ \text{(LTE)}_{Y_1} &= \left((Y_1)_t - \frac{(Y_1)_j^{n+1} - (Y_1)_j^n}{\psi_{Y_1}} \right) \\ &\quad - \left((Y_1)_{xx} - \frac{(Y_1)_{j+1}^{n+1} - 2(Y_1)_j^{n+1} + (Y_1)_{j-1}^{n+1}}{(\phi_{Y_1})_j^2} \right), \\ &\quad + (f_2(t, x, X, Y_1, Z) - f_2(t, x, X_j^n, (Y_1)_j^n, Z_j^n)), \\ \text{(LTE)}_Z &= \left(Z_t - \frac{Z_j^{n+1} - Z_j^n}{\psi_z} \right) - \left(Z_{xx} - \frac{Z_{j+1}^{n+1} - 2Z_j^{n+1} + Z_{j-1}^{n+1}}{(\phi_z)_j^2} \right) \\ &\quad + (f_3(t, x, X, Y_1, Z) - f_3(t, x, X_j^n, (Y_1)_j^n, Z_j^n)), \end{aligned} \right\} \quad (60)$$

where

$$\left. \begin{aligned} f_1(t, x, X, Y_1, Z) &= X \left(a\varphi_{P_x} - d_x - (a - d_x) \frac{X + Y_1 + Z}{k_h} \right), \\ f_1(t, x, X_j^n, (Y_1)_j^n, Z_j^n) &= X_j^n \left(a\varphi_{P_x} - d_x - (a - d_x) \frac{X_j^n + (Y_1)_j^n + Z_j^n}{k_h} \right), \\ f_2(t, x, X, Y_1, Z) &= (Y_1) \left(b_1\varphi_{P_{y_1}} \min \left(1, g \frac{Z - \alpha Y_1}{Y} \right) - d_1 - (b_1 - d_1) \frac{Y_1 + Z}{k_t} \right), \\ f_2(t, x, X_j^n, (Y_1)_j^n, Z_j^n) &= \\ &\quad (Y_1)_j^n \left(b_1\varphi_{P_{y_1}} \min \left(1, g \frac{Z_j^n - \alpha (Y_1)_j^n}{(Y_1)_j^n} \right) - d_1 - (b_1 - d_1) \frac{(Y_1)_j^n + Z_j^n}{k_t} \right), \\ f_3(t, x, X, Y_1, Z) &= c\varphi_{P_z} (\iota_{Y_1})_j (t_n - \tau) - d_z Z, \\ f_3(t, x, X_j^n, (Y_1)_j^n, Z_j^n) &= c\varphi_{P_z} (\iota_{Y_1})_j (t_n - \tau) - d_z Z_j^n. \end{aligned} \right\}$$

The first terms on the right hand side of equations in (60) satisfies

$$\begin{aligned}
& \left| X_t(t_n, x_j) - \frac{X_j^{n+1} - X_j^n}{\psi_X} \right| = \left| X_t(t_n, x_j) - \frac{X_j^{n+1} - X_j^n}{\Delta t} + \frac{X_j^{n+1} - X_j^n}{\Delta t} - \frac{X_j^{n+1} - X_j^n}{\psi_X} \right|, \\
& \leq \left| X_t(t_n, x_j) - \frac{X_j^{n+1} - X_j^n}{\Delta t} \right| + \left| \frac{X_j^{n+1} - X_j^n}{\Delta t} - \frac{X_j^{n+1} - X_j^n}{\psi_X} \right|, \\
& \leq \frac{\Delta t}{2} |X_{tt}(\xi, x_j)| + \left| X_t(\xi, x_j) + \frac{\Delta t}{2} X_{tt}(\xi, x_j) + \frac{(\Delta t)^2}{6} X_{ttt}(\xi, x_j) \right| \\
& \quad - \left| \frac{X_t(\xi, x_j) + \frac{\Delta t}{2} X_{tt}(\xi, x_j) + \frac{(\Delta t)^2}{6} X_{ttt}(\xi, x_j)}{1 + \frac{(d_x - a\varphi_{P_x})\Delta t}{2} + \frac{((d_x - a\varphi_{P_x})\Delta t)^2}{6}} \right|, \\
& \leq \frac{\Delta t}{2} C_X + \left| X_t(\xi, x_j) + \frac{\Delta t}{2} X_{tt}(\xi, x_j) + \frac{(\Delta t)^2}{6} X_{ttt}(\xi, x_j) \right| \\
& \quad - \left| \frac{X_t(\xi, x_j) + \frac{\Delta t}{2} X_{tt}(\xi, x_j) + \frac{(\Delta t)^2}{6} X_{ttt}(\xi, x_j)}{1 + \frac{(d_x - a\varphi_{P_x})\Delta t}{2} + \frac{((d_x - a\varphi_{P_x})\Delta t)^2}{6}} \right| \rightarrow 0 \text{ as } \Delta t \rightarrow 0, \\
& \left. \begin{aligned}
& \left| (Y_1)_t(t_n, x_j) - \frac{(Y_1)_j^{n+1} - (Y_1)_j^n}{\psi_{Y_1}} \right| \leq \left| (Y_1)_t(t_n, x_j) - \frac{(Y_1)_j^{n+1} - (Y_1)_j^n}{\psi_{Y_1}} \right| \\
& \quad + \left| \frac{(Y_1)_j^{n+1} - (Y_1)_j^n}{\Delta t} - \frac{(Y_1)_j^{n+1} - (Y_1)_j^n}{\psi_{Y_1}} \right|, \\
& \leq \frac{\Delta t}{2} |(Y_1)_{tt}(\xi, x_j)| + |(Y_1)_t(\xi, x_j) + \frac{\Delta t}{2} (Y_1)_{tt}(\xi, x_j)| \\
& \quad + \left| \frac{(\Delta t)^2}{6} (Y_1)_{ttt}(\xi, x_j) \right| - \left| \frac{(Y_1)_t(\xi, x_j) + \frac{\Delta t}{2} (Y_1)_{tt}(\xi, x_j) + \frac{(\Delta t)^2}{6} (Y_1)_{ttt}(\xi, x_j)}{1 - \frac{d_1 \Delta t}{2} + \frac{(d_1 \Delta t)^2}{6}} \right|, \\
& \leq \frac{\Delta t}{2} C_{Y_1} + \left| (Y_1)_t(\xi, x_j) + \frac{\Delta t}{2} (Y_1)_{tt}(\xi, x_j) + \frac{(\Delta t)^2}{6} (Y_1)_{ttt}(\xi, x_j) \right| \\
& \quad - \left| \frac{(Y_1)_t(\xi, x_j) + \frac{\Delta t}{2} (Y_1)_{tt}(\xi, x_j) + \frac{(\Delta t)^2}{6} (Y_1)_{ttt}(\xi, x_j)}{1 - \frac{d_1 \Delta t}{2} + \frac{(d_1 \Delta t)^2}{6}} \right| \rightarrow 0 \text{ as } \Delta t \rightarrow 0, \\
& \left| Z_t(t_n, x_j) - \frac{Z_j^{n+1} - Z_j^n}{\psi_Z} \right| = \left| Z_t(t_n, x_j) - \frac{Z_j^{n+1} - Z_j^n}{\Delta t} + \frac{Z_j^{n+1} - Z_j^n}{\Delta t} - \frac{Z_j^{n+1} - Z_j^n}{\psi_Z} \right|, \\
& \leq \left| Z_t(t_n, x_j) - \frac{Z_j^{n+1} - Z_j^n}{\Delta t} \right| + \left| \frac{Z_j^{n+1} - Z_j^n}{\Delta t} - \frac{Z_j^{n+1} - Z_j^n}{\psi_Z} \right|, \\
& \leq \frac{\Delta t}{2} |Z_{tt}(\xi, x_j)| + \left| Z_t(\xi, x_j) + \frac{\Delta t}{2} Z_{tt}(\xi, x_j) + \frac{(\Delta t)^2}{6} Z_{ttt}(\xi, x_j) \right| \\
& \quad - \left| \frac{Z_t(\xi, x_j) + \frac{\Delta t}{2} Z_{tt}(\xi, x_j) + \frac{(\Delta t)^2}{6} Z_{ttt}(\xi, x_j)}{1 - \frac{d_z \Delta t}{2} + \frac{(d_z \Delta t)^2}{6}} \right|, \\
& \leq \frac{\Delta t}{2} C_Z + \left| Z_t(\xi, x_j) + \frac{\Delta t}{2} Z_{tt}(\xi, x_j) + \frac{(\Delta t)^2}{6} Z_{ttt}(\xi, x_j) \right| \\
& \quad - \left| \frac{Z_t(\xi, x_j) + \frac{\Delta t}{2} Z_{tt}(\xi, x_j) + \frac{(\Delta t)^2}{6} Z_{ttt}(\xi, x_j)}{1 - \frac{d_z \Delta t}{2} + \frac{(d_z \Delta t)^2}{6}} \right| \rightarrow 0 \text{ as } \Delta t \rightarrow 0,
\end{aligned} \right\} \tag{61}
\end{aligned}$$

where $t_{n-1} \leq \xi \leq t_{n+1}$ in of each inequality in (61). The second term on the right-hand side of equations in (60) satisfies

$$\left. \begin{aligned}
& \left| X_{xx}(t_n, x_j) - \frac{X_{j+1}^{n+1} - 2X_j^{n+1} + X_{j-1}^{n+1}}{(\phi_X)_j^2} \right| \\
& \leq \left| X_{xx}(t_n, x_j) - \left(\frac{X_{j+1}^n - 2X_j^n + X_{j-1}^n}{(\Delta x)^2} \right) \right| \\
& + \left| \frac{X_{j+1}^n - 2X_j^n + X_{j-1}^n}{(\Delta x)^2} - \left(\frac{E_{j+1}^{n+1} - 2E_j^{n+1} + E_{j-1}^{n+1}}{(\phi_E)_j^2} \right) \right|, \\
& \leq \frac{(\Delta x)^2}{12} |X_{xxxx}(t_n, \zeta)| + \frac{(\Delta x)^2}{(\phi_X)^2} |X_{xx}(t_n, \zeta)| \\
& + \Delta t |X_{xxt}(\xi, x_j)| \rightarrow 0 \text{ as } (\Delta t, \Delta x) \rightarrow (0, 0), \\
& \left| (Y_1)_{xx}(t_n, x_j) - \frac{(Y_1)_{j+1}^{n+1} - 2(Y_1)_j^{n+1} + (Y_1)_{j-1}^{n+1}}{(\phi_{Y_1})_j^2} \right| \\
& \leq \left| (Y_1)_{xx}(t_n, x_j) - \left(\frac{(Y_1)_{j+1}^n - 2(Y_1)_j^n + (Y_1)_{j-1}^n}{(\Delta x)^2} \right) \right| \\
& + \left| \left(\frac{(Y_1)_{j+1}^n - 2(Y_1)_j^n + (Y_1)_{j-1}^n}{(\Delta x)^2} \right) - \left(\frac{(Y_1)_{j+1}^{n+1} - 2(Y_1)_j^{n+1} + (Y_1)_{j-1}^{n+1}}{(\phi_{Y_1})_j^2} \right) \right|, \\
& \leq \frac{(\Delta x)^2}{12} |(Y_1)_{xxxx}(t_n, \zeta)| + \frac{(\Delta x)^2}{(\phi_{(\Delta x)})^2} |(Y_1)_{xx}(t_n, \zeta)| \\
& + \Delta t |(Y_1)_{xxt}(\xi, x_j)| \rightarrow 0 \text{ as } (\Delta t, \Delta x) \rightarrow (0, 0), \\
& \left| Z_{xx}(t_n, x_j) - \frac{Z_{j+1}^{n+1} - 2Z_j^{n+1} + Z_{j-1}^{n+1}}{(\phi_Z)_j^2} \right| \\
& \leq \left| Z_{xx}(t_n, x_j) - \left(\frac{Z_{j+1}^n - 2Z_j^n + Z_{j-1}^n}{(\Delta x)^2} \right) \right| \\
& + \left| \left(\frac{Z_{j+1}^n - 2Z_j^n + Z_{j-1}^n}{(\Delta x)^2} \right) - \left(\frac{Z_{j+1}^{n+1} - 2Z_j^{n+1} + Z_{j-1}^{n+1}}{(\phi_Z)_j^2} \right) \right|, \\
& \leq \frac{(\Delta x)^2}{12} |Z_{xxxx}(t_n, \zeta)| + \frac{(\Delta x)^2}{(\phi_Z)^2} |Z_{xx}(t_n, \zeta)| \\
& + \Delta t |Z_{xxt}(\xi, x_j)| \rightarrow 0 \text{ as } (\Delta t, \Delta x) \rightarrow (0, 0),
\end{aligned} \right\} \tag{62}$$

where $x_{j-1} \leq \zeta \leq x_{j+1}$ in the third line of each inequality in (62), whereas by Lipschitz condition [2], we have the third terms in equation (60) satisfying

$$\begin{aligned}
& |f_1(t, x, X, Y_1, Z) - f_1(t, x, X_j^n, (Y_1)_j^n, Z_j^n)| \\
& \leq K_1 \max\{|X - X_j^n| + |Y_1 - (Y_1)_j^n| + |Z - Z_j^n|\}, \\
& |f_2(t, x, X, Y_1, Z) - f_2(t, x, X_j^n, (Y_1)_j^n, Z_j^n)| \\
& \leq K_2 \max\{|X - X_j^n| + |Y_1 - (Y_1)_j^n| + |Z - Z_j^n|\}, \\
& |f_3(t, x, X, Y_1, Z) - f_3(t, x, X_j^n, (Y_1)_j^n, Z_j^n)| \\
& \leq K_2 \max\{|X - X_j^n| + |Y_1 - (Y_1)_j^n| + |Z - Z_j^n|\},
\end{aligned} \tag{63}$$

where K_1, K_2, K_3 denote the Lipschitz constants.

Let

$$(e_X)_j^n = |X_j^n - X(t_n, x_j)|, \quad (e_{Y_1})_j^n = |(Y_1)_j^n - Y_1(t_n, x_j)|, \quad (e_Z)_j^n = |Z_j^n - Z(t_n, x_j)|,$$

then the inequalities in equation (63) becomes

$$\begin{aligned}
& |f_1(t, x, X, Y_1, Z) - f_1(t, x, X_j^n, (Y_1)_j^n, Z_j^n)| \leq K_1 \max\{(e_X)_j^n + (e_{Y_1})_j^n + (e_Z)_j^n\}, \\
& |f_2(t, x, X, Y_1, Z) - f_2(t, x, X_j^n, (Y_1)_j^n, Z_j^n)| \leq K_2 \max\{(e_X)_j^n + (e_{Y_1})_j^n + (e_Z)_j^n\}, \\
& |f_3(t, x, X, Y_1, Z) - f_3(t, x, X_j^n, (Y_1)_j^n, Z_j^n)| \leq K_3 \max\{(e_X)_j^n + (e_{Y_1})_j^n + (e_Z)_j^n\},
\end{aligned} \tag{64}$$

But we see that $(\Delta t, \Delta x) \rightarrow (0, 0)$ in equation (61) to (62), this implies that

$$(e_X)_j^n \rightarrow (e_X)_1^1 = 0, \quad (e_{Y_1})_j^n \rightarrow (e_{Y_1})_1^1 = 0, \quad (e_Z)_j^n \rightarrow (e_Z)_1^1 = 0. \tag{65}$$

The results that we obtained in equations (61), (62) to (65) prove that $(LTE)_X \rightarrow 0$, $(LTE)_{Y_1} \rightarrow 0$ and $(LTE)_Z \rightarrow 0$ as $\Delta t \rightarrow 0$ and $\Delta x \rightarrow 0$ and this proves the consistency of our FOFDM.

3.1.2. *Stability of the numerical method.* Substituting the exact solutions $X(t_n, x_j)$, $Y_1(t_n, x_j)$, $Z(t_n, x_j)$ instead of the approximations $\mathcal{X}_j^n, (\mathcal{Y}_1)_j^n, \mathcal{Z}_j^n$ in equation (58), we obtain

$$\left. \begin{aligned} P_X^{n+1} &= X_j^n \left(\frac{1}{\psi_X} + a\varphi_{P_x} - d_x - (a - d_x) \frac{X_j^n + (Y_1)_j^n + Z_j^n}{k_h} \right), \\ P_{Y_1}^{n+1} &= (Y_1)_j^n \left(\frac{1}{\psi_{Y_1}} + b_1\varphi_{P_{y_1}} \min \left(1, g \frac{Z_j^n - \alpha(Y_1)_j^n}{(Y_1)_j^n} \right) - d_1 \right. \\ &\quad \left. - (b_1 - d_1) \frac{(Y_1)_j^n + Z_j^n}{k_t} \right), \\ P_Z^{n+1} &= c\varphi_{P_z} (\iota_{Y_1})_j(t_n - \tau) + \left(\frac{1}{\psi_Z} - d_z \right) Z_j^n, \end{aligned} \right\} \quad (66)$$

Subtracting equation (66) from (58), taking the absolute values on both two sides and using equation in (65), we have

$$|e_{P_x}^{n+1}| \leq 0, |e_{P_{Y_1}}^{n+1}| \leq 0, |e_{P_z}^{n+1}| \leq 0, \quad (67)$$

where $e_{P_x}^{n+1} = \mathcal{P}_X(t_{n+1}, \cdot) - P_X(t_{n+1}, \cdot)$, and Similar notations are used in the second and third equation in (67).

This proves that the method is unconditionally stable.

Remark 1. For the model (49), we see that $(LTE)_X \rightarrow 0$, $(LTE)_{Y_1} \rightarrow 0$ and $(LTE)_Z \rightarrow 0$ as $\Delta t \rightarrow 0$ and $\Delta x \rightarrow 0$. Moreover, the method is unconditionally stable.

4. **Numerical results and discussions.** In this section, we present our numerical results with respect to the maximum proliferation rate of tumor cells and blood supply limitation indicator to help visualize when there are indeed limiting healthy and tumour cells growth. In order to investigate it, we implement our numerical method such that the stability conditions given in Theorems 2.1-2.2 are satisfied. Due to the unavailability of diffusion values, we set the diffusion constants $\mathcal{D}_x = 10^{-3}$, $\mathcal{D}_{y_1} = 20^{-4}$, $\mathcal{D}_z = 30^{-5}$. Following Elser et al. [7], we present our numerical results as follows.

TABLE 1. Parameter values[7]

$m = 20.00$	$n = 10.00$	$k_h = 10.00$
$k_t = 3.00$	$f = 0.6667$	$P = 150$
$m_1 = 20.00$	$\beta_1 = 1.00$	$c = 0.005$
$dz = 0.20$	$g = 100.00$	$\alpha = 0.05$

In Figure 1, we present the case when the birth rate of healthy cell are decreased than that of parenchyma cell ($a < b_1$ and dearth rate of healthy cell is increased than that of parenchyma cell ($d_x > d_1$) for (a) no treatment blocking phosphorus uptake by tumor cells, (b) lowered phosphorus P by 20%, (c) increased the time delay τ from 7 to 11 days and in (d) blocked tumor cell uptake of phosphorus by half.

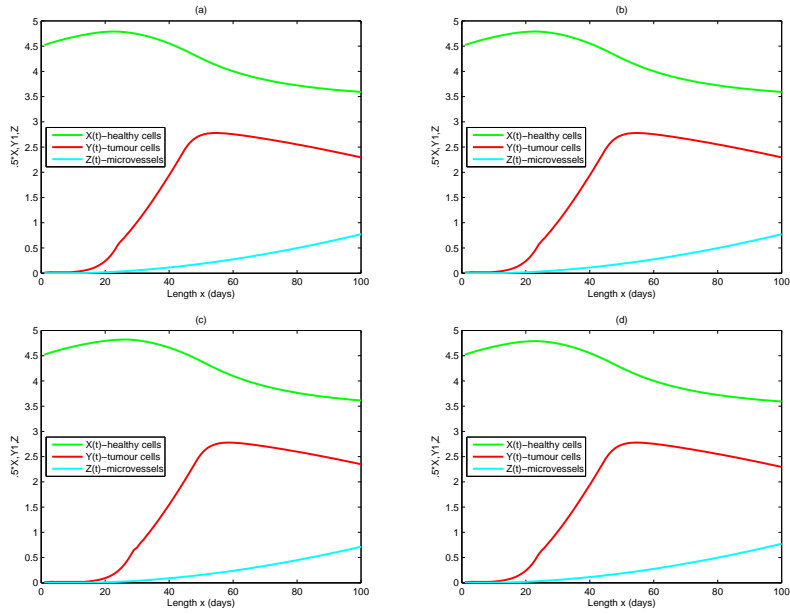


FIGURE 1. Numerical solution for the dynamics of homogeneous tumour growth model, when $a = 3, d_x = 2, b_1 = 6, d_1 = 0.5$.

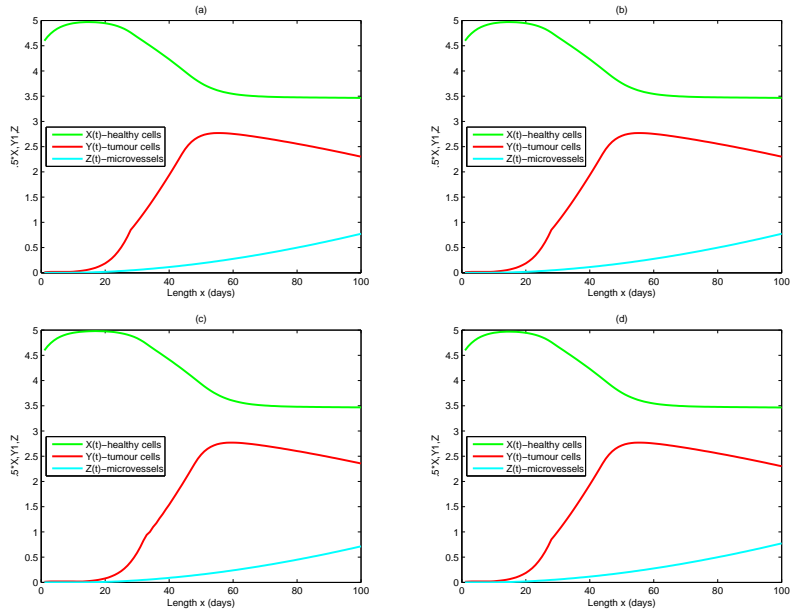


FIGURE 2. Numerical solution for the dynamics of homogeneous tumour growth model, when $a = 6, d_x = 1, b_1 = 6, d_1 = 1$.

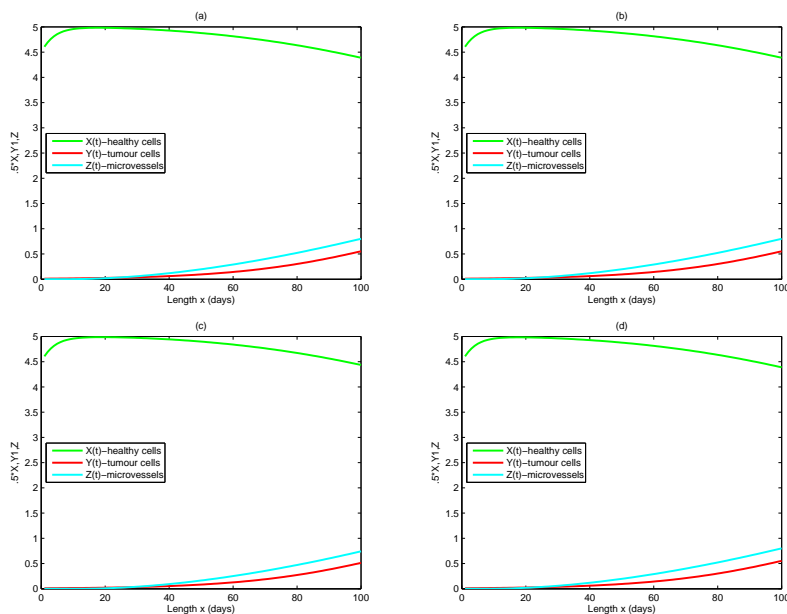


FIGURE 3. Numerical solution for the dynamics of homogeneous tumour growth model, when $a = 6$, $d_x = 0.5$, $b_1 = 3$, $d_1 = 2$.

In Figure 2, we present the case when the birth and death rates of healthy and parenchyma cells are equal ($a = b_1$ and $d_x = d_1$) for (a) no treatment blocking phosphorus uptake by tumor cells, (b) lowered phosphorus P by 20%, (c) increased the time delay τ from 7 to 11 days and in (d) blocked tumor cell uptake of phosphorus by half.

In Figure 3, we present the case when the birth of healthy cells are increased than that of a parenchyma cell ($a > b_1$) and increased death rate of healthy cells than that of a parenchyma cell ($d_x < d_1$) for (a) no treatment blocking phosphorus uptake by tumor cells, (b) lowered phosphorus P by 20%, (c) increased the time delay τ from 7 to 11 days and in (d) blocked tumor cells uptake of phosphorus by half.

The numerical solutions in Figure 1 present a slight growth of healthy cells and fast growth of tumour cell during the first 40 days from the infection date. We also see that after 40 days of infection, both cells converges to their steady states, with a slight decrease in their growth. This is due to the competition for resources among cells, presented by this case. After 40 days the process of vascularization starts to grow because the tumour cell has reached some genetically size. We also see that lowered phosphorus and blocked tumor cell uptake of phosphorus do not differ from the no treatment blocking phosphorus uptake by tumor cells, whereas the above features are postponed when we increased the time delay τ from 7 to 11 days.

The numerical solutions in Figure 2 present an increase growth of healthy cells and tumour cell during the first 40 days from the infection date. We also see that after 40 days of infection, both cells converges to their steady states, with a slight increase for healthy cells and a decrease growth of tumour cells. This is due to the competition for resources among cells presented by this case. After 40 days the

process of vascularization starts to grow because the tumour cell has reached some genetically size. We note that lowered phosphorus and blocked tumor cell uptake of phosphorus do not differ from the no treatment blocking phosphorus uptake by tumor cells, whereas the above features are postponed when we increased the time delay τ from 7 to 11 days.

The numerical solutions in Figure 3 present an increase growth of healthy cells as compare to the previous cases and a drastic decrease for tumour cell during the first 40 days from the infection date. After 40 days of infection, both cells converges to their respective steady states, with an increase of healthy cells and a decrease growth of tumour cell. This is due to the competition for resources among cells presented by this case. After 40 days the process of vascularization starts to grow, thus causing tumour cell to grow gradually. We note that lowered phosphorus and blocked tumor cell uptake of phosphorus do not differ from the no treatment blocking phosphorus uptake by tumor cell, whereas the above features are postponed when we increased the time delay τ from 7 to 11 days.

5. Conclusion. In this paper, we have considered the biological stoichiometry of tumour dynamics, vascularized by a single solid tumor growing within the confinement of an organ and the environment provided by an organ. We examined the presence of positive steady state solutions for all the possible limiting cases with respect to proliferation rate of tumour cell and determine the existence of Hopf bifurcation. Thus, our numerical solutions clearly present the fact that the biological stoichiometry of tumour dynamics is real and can contribute quite a great deal toward the development of therapeutically drugs which can contribute toward healing tumour and tumour related diseases. Thus, our approach in this work should serve as a first numerical attempt to incorporate the detailed effects of healthy and tumor cells competing for both space and essentials, but limiting nutrients within a host.

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