MATHEMATICAL ANALYSIS AND NUMERICAL SIMULATION OF A TUMOR-HOST MODEL WITH CHEMOTHERAPY APPLICATION

KOLADE M. OWOLABI*, KAILASH C. PATIDAR, ALBERT SHIKONGO

Department of Mathematics and Applied Mathematics,

University of the Western Cape, Cape Town 7535, South Africa

Abstract. In this paper, a system of non-linear quasi-parabolic partial differential system, modeling the chemotherapy application of spatial tumor-host interaction is considered. At some certain parameters, we derive the steady state of the anti-angiogenic therapy, baseline therapy and anti-cytotoxic therapy models as well as their local stability condition. We use the method of upper and lower solutions to show that the steady states are globally stable. Since the system of non-linear quasi-parabolic partial differential cannot be solved analytically, we formulate a robust numerical scheme based on the semi-fitted finite difference operator. Analysis of the basic properties of the method shows that it is consistent, stable and convergent. Our numerical results are in agreement with our theoretical findings.

Keywords: anti-angiogenic therapy; cytotoxic therapy; fitted operator numerical methods; stability analysis.

2010 AMS Subject Classification: 5L05, 65M06.

1. Introduction

A tumor is scientifically referred to as a neoplasm, or an abnormal tissue area that is either fluid-filled or solid in appearance. A tumor does not necessarily mean cancer, it can be classified

---

*Corresponding author

E-mail addresses: mkowolax@yahoo.com

into the benign type (which means non-progressive or cannot metastasize, for example, uterine fibroids and moles), pre-malignant (or pre-cancerous growth which include: actinic keratosis, dysplasia of the cervix, metaplasia of the lung and leukoplakia), or malignant (cancerous), and the malignant tumor which is a cancerous case. Record have shown that there are various types of tumors, which are made up of specific types of cancer cells; these include the carcinoma, sarcoma, lymphoma or leukemia, blastoma and germ cell tumor [13].

In practice, it requires an expert to differentiate between an ordinary tumor and a cancerous type. Its treatment can be classified into stages I-IV, the first two stages is called a low-grade tumor which can be treated by watchful monitoring or surgery. The high-grade class (III, IV) are malignant and can spread quickly from the affecting area to other surrounding tissues. Its treatment include the use of radiation therapy, chemotherapy, targeted therapy and tumor treating fields. According to statistics conducted on patients with the tumor related issues, chemotherapy approach forms the integral part of tumor treatment, because it requires administering drugs that can destroy the affected cancer cells by impeding their growth and reproduction. Chemotherapy delivery methods include: injection, orally (by mouth as a pill or liquid), intravenously (through infusion into a vein), topically (as a cream on the skin), direct placement (through a lumbar puncture or device placed under the scalp) [7].

In this paper, we consider the models derived by Hinow et al., in [6, *page 525 -527]*. The models consider cancer as a complex multiscale disease. Thus, to simplify their work toward finding an efficient healing of cancer, Hinow et al. derived a model for scenario of tumor growth only limited by intrinsic constraints such as oxygen supply and the surrounding stromal tissue, which they referred to as the baseline model. In order to cure such a complex multi-scale disease, Hinow et al., modified the baseline model to a cytostatic model in the sense that the drugs used are not toxic to the cells, but instead inhibit some mechanism essential for cell division or a specific function, which they referred to as an anti-angiogenic chemotherapy model and a drug that affects cells in the proliferative state which they referred to as cytotoxic chemotherapy model. Their findings are that when no treatment is applied to the model, their model reproduces a typical dynamics of early tumor growth and initially avascular tumor reaches a diffusion

limited size of the order of millimeters which initiates angiogenesis through the release of vascular endothelial growth factor (VEGF) secreted by hypoxic cells in the core of the tumor. They also stated that the VEGF stimulates endothelial cells to migrate towards the tumor and establishes a nutrient supply sufficient for sustained invasion. However, when they applied cytostatic treatment in the form of a VEGF-inhibitor, they found out that the treatment has the capability to reduce tumor mass. Moreover, they were able to determine that inhibition of endothelial cell proliferation as the more important of the two cellular functions targeted by the drug. On the other hand, considering the application of a cytotoxic drug as a diffusible substance entering the tissue from the blood vessels, they concluded that the drug can either reduce the tumor mass significantly or in fact accelerate the growth rate of the tumor. All these findings are based on experiments without mathematical analysis. Thus, to this end, we believe that mathematical analysis of their model can elaborate more clearly to the audience in this field. Thus, in the next paragraphs, we highlight their models.

Let t, x to denote time, space, w, n, h, a, m, f, g, c denote oxygen concentration, normoxic cells, hypoxic cells, apoptic cells, endothelial cells, extracellular matrix, angiogenic factor, concentration of a drug, and the density of all types of cells and matrix combined is

$$v = h + a + n + f + m.$$

For convenient of explaining the models, we group the dependent variables and diffusion terms into vector $\mathbf{u} = [w, n, h, a, m, f, g, c]^T$ and the diffusion coefficients $\mathbf{D} = [D_w, D_n \max\{n - v_c, 0\} + D_m, 0, 0, D_m, 0, D_g, D_c]^T$ respectively, then the cytotoxic chemotherapy (drug that affects cells in the proliferative state) and anti-angiogenic chemotherapy (also considered as cytostatic in the sense that the drugs used are not toxic to the cells, but instead inhibit some mechanism essential for cell division or a specific function) models in [6, *page 525-527*] was derived through the baseline model (scenario when tumor growth only limited by intrinsic constraints such as oxygen supply and the surrounding stromal tissue) which we rewrite in a vector form as

(1)
$$\frac{\partial \mathbf{u}}{\partial t}(x,t) - \frac{\partial}{\partial x}\left[\mathbf{D}, F\left(\mathbf{u}, \frac{\partial \mathbf{u}}{\partial x}\right)\right] = F(\mathbf{u}), \text{ with}$$

$$u_1(x,0) = 1.0, \quad u_2(x,0) = 0.93\exp(-200\xi^2), \quad u_3(x,0) = u_4(x,0) = 0.00,$$

$$u_5(x,0) = 0.01, \quad u_6(x,0) = 1 - u_2(\xi,0) - u_3(\xi,0) - 0.05, \quad u_7(x,0) = 0.00,$$

$$u_8(x,0) \in [0,1],$$

as the initial conditions, $F(\mathbf{u}) = F(w,n,h,a,m,f,g,c)$ and the boundary conditions for the reaction-diffusion system in equation (1) are the no flux-boundary conditions. Thus, for u_1 in equation (1) we have

(2)
$$\left. \begin{array}{l} \frac{\partial}{\partial x}[D_1, F\left(\mathbf{u}, \frac{\partial \mathbf{u}}{\partial x}\right)] = \frac{\partial}{\partial x}\left[D_1, \frac{\partial u_1}{\partial x}\right] \equiv D_w \frac{\partial^2 w}{\partial x^2}, \\ \\ F(\mathbf{u}) \equiv \alpha_w m(w_{\max} - w) - \beta_w(n+h+m)w - \gamma_w w, \end{array} \right\}$$

where, $D_w, \alpha_w, w_{\max}, \beta_w, \gamma_w$ denote the coefficient of oxygen diffusion, rate of diffusability of oxygen, maximum oxygen density, uptake rate of oxygen by normoxic, hypoxic, endothelial cells and loss rate of oxygen. The reason for the choice of the source term $\alpha_w m(w_{\max} - w)$ is that, at high environmental levels of oxygen, less oxygen is released through the vessel walls.

For u_2 in equation (1) we have

(3)
$$\left. \begin{array}{l} \frac{\partial}{\partial x}[D_2, F\left(\mathbf{u}, \frac{\partial \mathbf{u}}{\partial x}\right)] = \frac{\partial}{\partial x}\left((D_n \max\{n - v_c, 0\} + D_m)\frac{\partial n}{\partial x} - \chi_n n \frac{\partial f}{\partial x}\right), \\ \\ F(\mathbf{u}) \equiv \alpha_n n(v_{\max} - v) - \alpha_h \mathscr{H}(w_h - w)n + \frac{\alpha_h}{10}\mathscr{H}(w - w_h)h, \end{array} \right\}$$

where, $v_c, D_n \max\{n - v_c, 0\}n_x, D_m, \chi_n, \alpha_n, v_{\max}, w_h, \alpha_h, \mathscr{H}$ denote a threshold which adds to the dispersion of these cells through crowding-driven motion, nonlinear diffusion, random motility, haptotactic movement, rate of logistic growth, maximal density, critical value, rate of gain or loss, Heaviside function which is 1 for positive arguments and zero otherwise. We also see that the growth of normoxic cells levels off in regions where the sum of all cells and matrix approaches the maximal density $v_{\max}$. In the regions where the concentration of oxygen drops below a certain critical value w_h, normoxic cells enter the hypoxic class at a rate α_h and this transition process is reversible, and the reverse transition is denoted by the the reduced rate $\alpha_h/10$.

For u_3 in equation (1) we have

(4)
$$\left. \begin{array}{l} \frac{\partial}{\partial x}[D_3, F\left(\mathbf{u}, \frac{\partial \mathbf{u}}{\partial x}\right)] = 0, \\ F(\mathbf{u}) \equiv \alpha_h \mathscr{H}(w_h - w)n - \frac{\alpha_h}{10}\mathscr{H}(w - w_h)h - \beta_h \mathscr{H}(w_a - w)h, \end{array} \right\}$$

The first and the second terms are in equation (14) are dictated by conservation of mass and correspond to terms in equation (13). The third term in equation (14) denotes the transition of

hypoxic cells to apoptotic cells at rate β_h as the level of oxygen falls below a second threshold, which is $w_a < w_h$. In [6, *page 526*] is reported that hypoxic cells are less active in general due to reduced availability of oxygen and other nutrients and thus, they assumed that lack of energy causes them to be immobile.

For u_4 in equation (1) we have

$$
\left.
\begin{aligned}
&\frac{\partial}{\partial x}[D_4, F\left(\mathbf{u}, \frac{\partial \mathbf{u}}{\partial x}\right)] = 0, \\
&F(\mathbf{u}) \equiv \beta_h \mathscr{H}(w_a - w)h,
\end{aligned}
\right\}
$$
(5)

The first term denotes the transition from hypoxic class to apoptic class.

For u_5 in equation (1) we have

$$
\left.
\begin{aligned}
&\frac{\partial}{\partial x}[D_5, F\left(\mathbf{u}, \frac{\partial \mathbf{u}}{\partial x}\right)] = \frac{\partial}{\partial x}\left(D_m \frac{\partial m}{\partial x} - m\chi_m \frac{\partial g}{\partial x}\right), \\
&F(\mathbf{u}) \equiv \alpha_m mg(v_{\max} - v),
\end{aligned}
\right\}
$$
(6)

where, D_m denotes the random motility for endothelial cells and endothelial cells respond via chemotaxis to gradients of angiogenic factor and this require the presence of angiogenic factor for proliferation. Proliferation is capped by the total density of cells. The proliferation constant for endothelial cells is α_m.

For u_6 in equation (1) we have

$$
\left.
\begin{aligned}
&\frac{\partial}{\partial x}[D_6, F\left(\mathbf{u}, \frac{\partial \mathbf{u}}{\partial x}\right)] = 0, \\
&F(\mathbf{u}) \equiv -\beta_f nf,
\end{aligned}
\right\}
$$
(7)

where the tissue matrix is degraded by the tumor cells according to a mass-action law with rate constant β_f.

For u_7 in equation (1) we have

$$
\left.
\begin{aligned}
&\frac{\partial}{\partial x}[D_7, F\left(\mathbf{u}, \frac{\partial \mathbf{u}}{\partial x}\right)] = D_g \frac{\partial^2 g}{\partial x^2}, \\
&F(\mathbf{u}) \equiv \alpha_g h - \beta_g mg,
\end{aligned}
\right\}
$$
(8)

where, D_g denotes diffusion coefficient, also see that angiogenic factor is produced by hypoxic cells (alone) at rate α_g and consumed by endothelial cells with a mass-action coefficient of β_g.

To ensure that they model is universal, Hinow et al., dimensionelise the baseline model (see in [6, *page 538-539*]) and the dimensionless baseline model is

$$\frac{\partial w}{\partial t}(x,t) - D_w\frac{\partial^2 w}{\partial x^2} = \alpha_w m(1-w) - \beta_w(n+h+m)w - \gamma_w w,$$

$$\frac{\partial n}{\partial t}(x,t) - \frac{\partial}{\partial x}\left((D_n\max\{n-v_c,0\}+D_m)\frac{\partial n}{\partial x} - \chi_n n\frac{\partial f}{\partial x}\right) = \alpha_n n(v_{\max}-v)$$

$$-\alpha_h\mathcal{H}(w_h-w)n + \frac{\alpha_h}{10}\mathcal{H}(w-w_h)h - \gamma_n nc,$$

$$\frac{\partial h}{\partial t}(x,t) = \alpha_h\mathcal{H}(w_h-w)n - \frac{\alpha_h}{10}\mathcal{H}(w-w_h)h - \beta_h\mathcal{H}(w_a-w)h,$$

(9)

$$\frac{\partial a}{\partial t}(x,t) = \beta_h\mathcal{H}(w_a-w)h + \gamma_n nc,$$

$$\frac{\partial m}{\partial t}(x,t) - \frac{\partial}{\partial x}\left(D_m\frac{\partial m}{\partial x} - m\chi_m\frac{\partial g}{\partial x}\right) = \alpha_m mg(v_{\max}-v),$$

$$\frac{\partial f}{\partial t}(x,t) = -\beta_f nf,$$

$$\frac{\partial g}{\partial t}(x,t) - D_g\frac{\partial^2 g}{\partial x^2} = \alpha_g h - \beta_g mg.$$

When

$$\alpha_m \rightarrow \frac{\alpha_m}{10},$$
$$\chi_m \rightarrow \frac{\chi_m}{10}$$

in equation (9), the baseline model becomes the anti-angiogenic chemotherapy model.

However, when a drug that affects cells in the proliferative state is introduced then the normoxic cells are driven into apoptosis at a rate proportional to the drug concentration, then the baseline becomes the cytotoxic chemotherapy model. This implies that the reaction function equation in (13) becomes

(10) $$F(\mathbf{u}) \equiv \alpha_n n(v_{\max}-v) - \alpha_h\mathcal{H}(w_h-w)n + \frac{\alpha_h}{10}\mathcal{H}(w-w_h)h - \gamma_n nc,$$

with rate constant $\gamma > 0$, whereas, in order to balance the loss of normoxic cells, the reaction function for apoptotic cells in equation (15) is amended accordingly to

$$(11) \qquad F(\mathbf{u}) \equiv \beta_h \mathscr{H}(w_a - w)h + \gamma_n nc,$$

and whenever, the concentration of the drug denoted by $c \in [0,1]$ which is assumed to be delivered through blood infusion and thus enters the tissue from the blood stream. The production rate of the drug is therefore proportional to the density of endothelial cells, which implies that regions with higher vascular density will experience a higher concentration of the drug. Hence it is described by a reaction-diffusion equation similar to that of oxygen as

$$(12) \qquad \left.\begin{array}{c} \frac{\partial}{\partial x}[D_8, F\left(\mathbf{u}, \frac{\partial \mathbf{u}}{\partial x}\right)] = \frac{\partial}{\partial x}\left[D_8, \frac{\partial u_8}{\partial x}\right] \equiv D_c \frac{\partial^2 c}{\partial x^2}, \\[2ex] F(\mathbf{u}) \equiv \alpha_c(t)m(1-c) - \gamma_c c - k\gamma_n nc, \end{array}\right\}$$

The drug diffuses at a constant rate D_c in the tissue and decays at a constant rate $_c$, it also affects the normoxic cells in such a way that it is consumed at a rate $k\gamma_n$ when it kills normoxic cells. Instead of looking at a constant drug supply Hinow et al.,in [6, *page 532*] included a scheduling of the drug by letting the production rate $\alpha_c(t) > 0$

$$\alpha_c(t) = 100 \sum_{k=0}^{5} \exp(-4(t - (200 + 2k))^2),$$

be a time-dependent function, corresponding to the drug being delivered to the tissue.

It is well known fact that many research work have been done with regard to solve dynamic models either analytically or numerically. For instance Cristini et al., [4] developed a thermodynamically consistent mixture model for avascular solid tumor growth which takes into account the effects of cell-to-cell adhesion, and taxis inducing chemical and molecular species. They showed that their model is well-posed and the governing equations are of Cahn-Hilliard type. To solve the governing equations, they developed a numerical algorithm based on an adaptive Cartesian block-structured mesh refinement scheme and found out that the their numerical solutions presented that taxis may play a role in tumor invasion, because when nutrient plays the role of a chemoattractant, they found out that diffusional instability is exacerbated by nutrient

gradients. Accordingly, they also believed that their model is capable of describing complex invasive patterns observed in experiments.

However, based on biological and ecological fields, Tuan et al., in [20] studied the identification of the population density of a logistic equation backwards in time associated with non-local diffusion and nonlinear reaction. Since their original model is ill-posed, they applied the quasi-reversibility method to convert their model to a stable approximation model. Their numerical results presented the convergence and stability of the regularized solution for the backward parabolic problem with non-local diffusion and nonlinear reaction term.

However, some of the solution to a model is considered as a cure to a tumor disease, because they are compared to experimental data in most cases, see in [3, 23]. Due to limited availability of the literature, we are only able to mention a few.

Since, Hinow et al.,[6] presented their results without presenting their stability analysis of the models in their work in [6]. Thus, we believe that they were not able to explain their results by referring to direct mathematical analysis. This, we believe has undermined the qualitative features of the underlying mathematical models at hand. Therefore in this paper, our aim is to present our mathematical analysis of the models on their merits and establish the stability condition for each model. We then use stability conditions to present our results. Due to the non-linearities of terms in the models, we construct a reliable numerical method capable of capturing the qualitative features of these models.

Thus, it is a well known fact that solving the problems like the one in equation (1) with the standard finite difference methods (SFDMs) has limitations. That is, explicit methods finite difference methods (EFDMs), can solve such differential equations with low computational cost, with very small stability regions, which in turn implies severe restrictions on the meshes sizes, which are required in order to achieve the desired results. On the other hand, the implicit finite difference methods (IFDMs) do solve such differential equations with wider stability regions as compared to the EFDMS. However, their associated computational complexity can achieve only one order as compared to EFDMs that use the same number of stages [2].

The rest of the paper is organized as follows. Mathematical analysis of the main model is presented in Section 2. A robust numerical scheme based on the semi-fitted finite difference

technique is formulated in Section 3, analysis of the basic properties of this scheme is also examined for convergence. To justify the effectiveness of the proposed schemes, we present some numerical results in Section 4. Section 5 concludes the paper.

2. Mathematical analysis of the models

In this work, our major attention is on the baseline, anti-angiogenic and cytotoxic chemotherapy models. We shall adapt linear stability analysis method to discuss the general dynamics of each model. At the steady state, the cytotoxic chemotherapy model in equation (1), becomes

$$
\begin{aligned}
& \alpha_w m(1-w) - \beta_w(n+h+m)w - \gamma_w w = 0, \\[2ex]
& \alpha_n n(v_{\max} - v) - \alpha_h \mathscr{H}(w_h - w)n + \tfrac{1}{10}\alpha_h \mathscr{H}(w - w_h)h - \gamma_n nc = 0, \\[2ex]
& \alpha_h \mathscr{H}(w_h - w)n - \tfrac{1}{10}\alpha_h \mathscr{H}(w - w_h)h - \beta_h \mathscr{H}(w_a - w)h = 0, \\[2ex]
& \beta_h \mathscr{H}(w_a - w)h + \gamma_n nc = 0, \\[2ex]
& \alpha_m mg(v_{\max} - v) = 0, \\[2ex]
& -\beta_f nf = 0, \\[2ex]
& \alpha_g h - \beta_g mg = 0, \\[2ex]
& \gamma_c c - k\gamma_n nc = 0,
\end{aligned}
$$

(13)

where we see that the steady states of the baseline and anti-angiogenic models are the same. Solving the system of nonlinear equations in equation (13), we obtain

(14) $\qquad w^* = \dfrac{\alpha_w m^*}{\alpha_w + \beta_w m^* + \gamma_w}, \, m^* = v_{\max}, \, n^* = h^* = a^* = f^* = g^* = 0, \, c^* > 0.$

We see the oxygen and endothelial cells staedy states (w^* and m^*) are positive for the baseline, anti-angiogenic and cytotoxic chemotherapy models. Consequently, the hypoxic, apoptic cells'

, angiogenic factor (VEGF) and the extra-cellular matrix steady states are zero. On the other hand, when a host is tumor free, we find that

$$(15) \qquad\qquad w^* = 0, \, f^* = v_{max},$$

which implies that the extra-cellular matrix ($\underline{f}$) in all three models is well and healthy. We also see that the oxygen cells' steady state is zero, rendering the tumor free case unworthy to investigate.

Therefore, for the baseline, anti-angiogenic and cytotoxic chemotherapy models, we have the uniform steady states as

$$(16) \qquad
\begin{bmatrix} w^* \\ n^* \\ h^* \\ a^* \\ m^* \\ f^* \\ g^* \\ c^* \end{bmatrix}
=
\begin{bmatrix} \frac{\alpha_w v_{max}}{\alpha_w + \beta_w v_{max} + \gamma_w} \\ 0 \\ 0 \\ 0 \\ v_{max} \\ 0 \\ 0 \end{bmatrix}
,\;
\begin{bmatrix} \frac{\alpha_w m^*}{\alpha_w + \beta_w v_{max} + \gamma_w} \\ 0 \\ 0 \\ 0 \\ v_{max} \\ 0 \\ 0 \end{bmatrix}
,\;
\begin{bmatrix} \frac{\alpha_w v_{max}}{\alpha_w + \beta_w v_{max} + \gamma_w} \\ 0 \\ 0 \\ 0 \\ v_{max} \\ 0 \\ 0 \\ c^* > 0 \end{bmatrix}.$$

Stability of the steady states in equation (16) can be investigated from the corresponding homogeneous baseline, anti-angiogenic and cytotoxic chemotherapy models. Thus, extracting the Jacobian matrices for all three models, from the system in equation (1), we obtain the non-zero entries of the Jacobian matrices for all the three models evaluated at the critical points as

$$
\begin{aligned}
J_{1,1} &= -\alpha_w m^* - \beta_w m^* - \gamma_w, \, J_{1,2} = J_{1,3} = -\beta_w w^*, \, J_{1,5} = \alpha_w(1 - w^*) - \beta_w w^*, \\
J_{2,2} &= \alpha_n v_{max} - \alpha_h \mathscr{H}(w_h - w^*) - \gamma_n c^*, \, J_{2,3} = \frac{\alpha_h}{10}\mathscr{H}(w^* - w_h), \, J_{3,2} = \alpha_h \mathscr{H}(w_h - w^*), \\
J_{3,3} &= -\frac{\alpha_h}{10}\mathscr{H}(w^* - w_h) - \beta_h \mathscr{H}(w_a - w^*), \, J_{4,2} = \gamma_n c^*, \, J_{4,3} = \beta_h \mathscr{H}(w_a - w^*), \\
J_{7,3} &= \alpha_g, \, J_{7,5} = -\beta_g m^*, \, J_{8,2} = -k\gamma_n c^*, \, J_{8,8} = -\gamma_c,
\end{aligned}
\tag{17}
$$

which clearly reduces to the characteristic equation of the form

$$(18) \qquad\qquad \lambda^2 - \text{tr}(J_{2\times2})\lambda + \det(J_{2\times2}) = 0,$$

where

$$
\begin{aligned}
\operatorname{tr}(J_{2\times2}) &= J_{2,2} + J_{3,3}, \\
&= \alpha_n v_{\max} - \alpha_h \mathcal{H}(w_h - w) - \gamma_n c^* - \tfrac{\alpha_h}{10}\mathcal{H}(w^* - w_h) - \beta_h \mathcal{H}(w_a - w^*), \\
\det(J_{2\times2}) &= (J_{2,2}) \times (J_{3,3}) - (J_{2,3}) \times (J_{3,2}), \\
&\quad - (\alpha_n v_{\max} - \alpha_h \mathcal{H}(w_h - w^*) - \gamma_n c^*)\left(\tfrac{\alpha_h}{10}\mathcal{H}(w^* - w_h) + \beta_h \mathcal{H}(w_a - w^*)\right) \\
&\quad - \tfrac{\alpha_h^2}{10}\mathcal{H}(w_h - w^*)\mathcal{H}(w^* - w_h).
\end{aligned}
\left.\vphantom{\begin{aligned}1\\2\\3\\4\\5\end{aligned}}\right\}
$$

The steady states in equation (16) are asymptotically stable if and only if the trace and the determinant in equation (19) is negative and postive respectively, ([8]). This implies that $\operatorname{tr}(J_{2\times2}) < 0$ gives

$$
(19) \qquad \alpha_n v_{\max} < \alpha_h \mathcal{H}(w_h - w^*) + \gamma_n c^* + \frac{\alpha_h}{10}\mathcal{H}(w^* - w_h) + \beta_h \mathcal{H}(w_a - w^*),
$$

and $\det(J_{2\times2}) > 0$ gives

$$
-(\alpha_n v_{max} - \alpha_h \mathcal{H}(w_h - w^*) - \gamma_n c^*)\left(\frac{\alpha_h}{10}\mathcal{H}(w^* - w_h) + \beta_h \mathcal{H}(w_a - w^*),\right)
$$

$$
-\frac{\alpha_h^2}{10}\mathcal{H}(w_h - w^*)\mathcal{H}(w^* - w_h) > 0,
$$

$$
(20) \quad \Rightarrow \alpha_n v_{\max} < \alpha_h \mathcal{H}(w_h - w^*) + \gamma_n c^* - \frac{\frac{\alpha_h^2}{10}\mathcal{H}(w_h - w^*)\mathcal{H}(w^* - w_h)}{\left(\frac{\alpha_h}{10}\mathcal{H}(w^* - w_h) + \beta_h \mathcal{H}(w_a - w^*)\right)}.
$$

Thus, for the baseline model, we have from equations (19-20) that

$$
(21) \qquad
\begin{aligned}
&\alpha_n v_{\max} < \alpha_h \mathcal{H}(w_h - w^*) + \tfrac{\alpha_h}{10}\mathcal{H}(w^* - w_h) + \beta_h \mathcal{H}(w_a - w^*), \\
&\alpha_n v_{\max} < \alpha_h \mathcal{H}(w_h - w^*) - \frac{\frac{\alpha_h^2}{10}\mathcal{H}(w_h-w^*)\mathcal{H}(w^*-w_h)}{\left(\frac{\alpha_h}{10}\mathcal{H}(w^*-w_h) + \beta_h \mathcal{H}(w_a-w^*)\right)},
\end{aligned}
\left.\vphantom{\begin{aligned}1\\2\end{aligned}}\right\}
$$

which implies that the product of the logistic growth of the normoxic cells with the maximal density is bounded by the rates of the transitions of normoxic cells into hypoxic cells (and vice versa), hypoxic cells into apoptic cells (vice-versa).

Hence, the baseline model stability makes the anti-angiogenic chemotherapy model uncoditional stable. Consequently, the cytotoxic chemotherapy model asymptotic stability is

$$
(22) \qquad
\begin{aligned}
&\alpha_n v_{\max} < \gamma_n c^* + \alpha_h \mathcal{H}(w_h - w^*) + \tfrac{\alpha_h}{10}\mathcal{H}(w^* - w_h) + \beta_h \mathcal{H}(w_a - w^*), \\
&\alpha_n v_{\max} < \gamma_n c^* + \alpha_h \mathcal{H}(w_h - w^*) - \frac{\frac{\alpha_h^2}{10}\mathcal{H}(w_h-w^*)\mathcal{H}(w^*-w_h)}{\left(\frac{\alpha_h}{10}\mathcal{H}(w^*-w_h) + \beta_h \mathcal{H}(w_a-w^*)\right)},
\end{aligned}
\left.\vphantom{\begin{aligned}1\\2\end{aligned}}\right\}
$$

which implies that the product of the logistic growth of the normoxic cells with the maximal density is bounded by the sum of death rate of the normoxic cells (due to the presence of the drug), rates of the transitions of normoxic cells into hypoxic cells (and vice versa), hypoxic cells into apoptic cells (vice-versa). **Remark 2.1** *The stability conditions present the following facts:*

(a) *heavyweight functions should not be all zero for the baseline model to exists.*

(b) *the stability conditions mainly only affects maximal density, normoxic, hypoxic cells and the cytotoxic drug.*

(c) *the apoptic cells and agiogenic factor are not affected by the stability conditions.*

Global stability of the steady states

In this segment, we mainly prove that the equilibrium points in equation (16) are globally asymptotically stable with the upper and lower solution method in [14, 15]. Denoting the reaction functions in equation (1) by $l_j(w,n,h,a,m,f,g,c)$ for $j = 1,2,3,4,5,6,7,8$, then from equation (1) we let

$$
(23) \quad \left.
\begin{aligned}
l_1 &= \alpha_w m(1-w) - \beta_w(n+h+m)w - \gamma_w w, \\
l_2 &= \alpha_n n(v_{max}-v) - \alpha_h \mathcal{H}(w_h-w)n + \tfrac{1}{10}\alpha_h \mathcal{H}(w-w_h)h - \gamma_n nc, \\
l_3 &= \alpha_h \mathcal{H}(w_h-w)n - \tfrac{1}{10}\alpha_h \mathcal{H}(w-w_h)h - \beta_h \mathcal{H}(w_a-w)h, \\
l_4 &= \beta_h \mathcal{H}(w_a-w)h + \gamma_n nc, \\
l_5 &= \alpha_m mg(v_{\max}-v), \\
l_6 &= -\beta_f nf, \\
l_7 &= \alpha_g h - \beta_g mg, \\
l_8 &= 100\sum_{k=0}^{5}\exp(-4(t-(200+2k))^2)m(1-c) - \gamma_c c - k\gamma_n nc,
\end{aligned}
\right\}
$$

and let $U \subset \mathbb{R}_+^8$ such that $U = \{\mathbf{u} \in \mathbb{R}_+^8 : \underline{\mathbf{u}} \le 0 \le \bar{\mathbf{u}}\}$ and K_j be any positive constant satisfying

$$
\begin{aligned}
K &\ge \max\{K_w, K_n, K_h, K_a, K_m, K_f, K_g, , K_c\} \\
&\ge \max\left\{\frac{-\partial l_j}{\partial u_j} : \mathbf{u} = (w,n,h,a,m,f,g,c) \in S\right\}, \quad j = 1,2,3,4,5,6,7,8,
\end{aligned}
$$

then we have the following results (see [22]).

Lemma 2.1. *Let*

(24)
$$
\left.
\begin{aligned}
&\frac{\partial w}{\partial t}(x,t) - D_w \frac{\partial^2 w}{\partial x^2} \leq K_w, \\
&\frac{\partial n}{\partial t}(x,t) - \frac{\partial}{\partial x}\left((D_n \max\{n - v_c, 0\} + D_m)\frac{\partial n}{\partial x} - \chi_n n \frac{\partial f}{\partial x} \right) \leq K_n, \\
&\frac{\partial h}{\partial t}(x,t) \leq K_h, \\
&\frac{\partial a}{\partial t}(x,t) \leq K_a, \\
&\frac{\partial m}{\partial t}(x,t) - \frac{\partial}{\partial x}\left(D_m \frac{\partial m}{\partial x} - m\chi_m \frac{\partial g}{\partial x} \right) \leq K_m, \\
&\frac{\partial f}{\partial t}(x,t) \leq K_f, \\
&\frac{\partial g}{\partial t}(x,t) - D_g \frac{\partial^2 g}{\partial x^2} \leq K_g, \\
&\frac{\partial c}{\partial t}(x,t) - D_c \frac{\partial^2 c}{\partial x^2} \leq K_c
\end{aligned}
\right\}
$$

then

$$
\begin{aligned}
\lim_{t\to\infty} w(x,t) &= K_w, \ \lim_{t\to\infty} n(x,t) = K_n, \ \lim_{t\to\infty} h(x,t) = K_h, \ \lim_{t\to\infty} a(x,t) = K_a, \\
\lim_{t\to\infty} m(x,t) &= K_m, \ \lim_{t\to\infty} f(x,t) = K_f, \ \lim_{t\to\infty} g(x,t) = K_g, \ \lim_{t\to\infty} c(x,t) = K_c.
\end{aligned}
$$

Theorem 2.1. *The equilibrium points in equation (16) are globally asymptotically stable.*

Proof. From the maximum principle of parabolic equations, it is known that for any initial value $(w_0(t,x), n_0(t,x), h_0(t,x), a_0(t,x), m_0(t,x), f_0(t,x), g_0(t,x), c_0(t,x)) > (0,0,0,0,0)$ the corresponding non-negative solution $(w(t,x), n(t,x), h(t,x), a(t,x), m(t,x), f(t,x), g(t,x), c(t,x))$ is strictly positive for $t > 0$. Since the equilibrium points in equation (16) are non-negative, then let $\varepsilon_0 \in (0,1)$. Then according to Lemma (2.1) and the comparison principle of parabolic equations, there exists $t_1 > t_0 > 0$ such that, for any $t > t_1$,

(25)
$$
\left.
\begin{aligned}
w(x,t) &\leq K_w + \varepsilon_0 := \bar{w}(x,t), \\
n(x,t) &\leq K_n + \varepsilon_0 := \bar{n}(x,t), \\
h(x,t) &\leq K_h + \varepsilon_0 := \bar{h}(x,t), \\
a(x,t) &\leq K_a + \varepsilon_0 := \bar{a}(x,t), \\
m(x,t) &\leq K_m + \varepsilon_0 := \bar{m}(x,t), \\
f(x,t) &\leq K_f + \varepsilon_0 := \bar{f}(x,t), \\
g(x,t) &\leq K_g + \varepsilon_0 := \bar{g}(x,t), \\
c(x,t) &\leq K_c + \varepsilon_0 := \bar{c}(x,t),
\end{aligned}
\right\}
$$

and

$$
\left.
\begin{aligned}
w(x,t) &\geq K_w - \varepsilon_0 := \underline{w}(x,t), \\
n(x,t) &\geq K_n - \varepsilon_0 := \underline{n}(x,t), \\
h(x,t) &\geq K_m - \varepsilon_0 := \underline{m}(x,t), \\
a(x,t) &\geq K_a - \varepsilon_0 := \underline{a}(x,t), \\
m(x,t) &\geq K_m - \varepsilon_0 := \underline{m}(x,t), \\
f(x,t) &\geq K_f - \varepsilon_0 := \underline{f}(x,t), \\
g(x,t) &\geq K_g - \varepsilon_0 := \underline{g}(x,t), \\
c(x,t) &\geq K_c - \varepsilon_0 := \underline{c}(x,t).
\end{aligned}
\right\}
$$

(26)

Thus, for $t > t_0$, it is possible to obtain

$$
\begin{aligned}
\underline{w}(x,t) &\leq w(x,t) \leq \bar{w}(x,t), \underline{n}(x,t) \leq n(x,t) \leq \bar{n}(x,t), \\
\underline{h}(x,t) &\leq h(x,t) \leq \bar{h}(x,t), \underline{a}(x,t) \leq a(x,t) \leq \bar{a}(x,t), \\
\underline{m}(x,t) &\leq m(x,t) \leq \bar{m}(x,t), \underline{f}(x,t) \leq f(x,t) \leq \bar{f}(x,t), \\
\underline{g}(x,t) &\leq g(x,t) \leq \bar{g}(x,t), \underline{c}(x,t) \leq c(x,t) \leq \bar{c}(x,t).
\end{aligned}
$$

(27)

Since $l_j(w,n,h,a,m,f,g,c)$ in equation (26) is a C^1 function of w,n,h,a,m,f,g,c, where l_1 is quasi-monotone non-increasing in n,h,a,m,f,g,c, l_2 is mixed quasi-monotone in w,h,a,m,f,g,c, l_3 is quasi-monotone non-decreasing in w,n,a,m,f,g,c, l_4 is mixed quasi-monotone in w,n,h,m,f,g,c, h_5 is mixed quasi-monotone in w,n,h,a,f,g,c, l_6 is quasi-monotone non-decreasing in w,n,h,a,m,g,c, l_7 is mixed quasi-monotone in w,n,h,a,m,f,c and l_8 is mixed quasi-monotone in w,n,h,a,m,f,g, then by the method of upper and lower solutions we know that the system in (1) has a unique global non-negative solution w,n,h,a,m,f,g,c, [14]. Thus,

(28) $\underline{w},\bar{w},\underline{n},\bar{n},\underline{h},\bar{h},\underline{a},\bar{a},\underline{m},\bar{m},\underline{f},\bar{f},\underline{g},\bar{g},\underline{c},\bar{c},$

satisfy

$$
\left.
\begin{aligned}
&\alpha_w \underline{m}(1-\bar{w}) - \beta_w(\underline{n}+\underline{h}+\underline{m})\bar{w} - \gamma_w \bar{w} \geq 0 \geq \alpha_w \bar{m}(1-\underline{w}) \\
&-\beta_w(\bar{n}+\bar{h}+\bar{m})\underline{w} - \gamma_w \underline{w}, \\[2ex]
&\alpha_n \bar{n}(v_{max} - (\underline{h}+\underline{a}+\bar{n}+\underline{f}+\underline{m})) - \alpha_h \mathscr{H}(w_h - \bar{w})\bar{n} \\
&+\frac{\alpha_h}{10}\mathscr{H}(\underline{w} - w_h)h - \gamma_n \bar{n}\underline{c} \geq 0 \geq \alpha_n \underline{n}(v_{max} - (\bar{h}+\bar{a}+\underline{n}+\bar{f}+\bar{m})) \\
&-\alpha_h \mathscr{H}(w_h - \bar{w})\underline{n} + \frac{\alpha_h}{10}\mathscr{H}(\bar{w} - w_h)h - \gamma_n \underline{n}\bar{c}, \\[2ex]
&\alpha_h \mathscr{H}(w_h - \bar{w})\bar{n} - \frac{\alpha_h}{10}\mathscr{H}(\bar{w} - w_h)\bar{h} - \beta_h \mathscr{H}(w_a - \bar{w})\bar{h} \geq 0 \geq \alpha_h \mathscr{H}(w_h - \underline{w})\underline{n} \\
&-\frac{\alpha_h}{10}\mathscr{H}(\underline{w} - w_h)\underline{h} - \beta_h \mathscr{H}(w_a - \underline{w})\underline{h}, \\[2ex]
&\beta_h \mathscr{H}(w_a - \underline{w})\underline{h} + \gamma_n nc \geq 0 \geq \beta_h \mathscr{H}(w_a - \bar{w})\bar{h} + \gamma_n \bar{n}\bar{c}, \\[2ex]
&\alpha_m \bar{m}\underline{g}(v_{max} - (\underline{h}+\underline{a}+\underline{n}+\underline{f}+\bar{m})) \geq 0 \geq \alpha_m \underline{m}\bar{g}(v_{max} - (\bar{h}+\bar{a}+\bar{n}+\bar{f}+\underline{m})), \\[2ex]
&-\beta_f \bar{n}\bar{f} \geq 0 \geq -\beta_f \underline{n}\underline{f}, \\[2ex]
&\alpha_g \underline{h} - \beta_g \underline{m}\bar{g} \geq 0 \geq \alpha_g \bar{h} - \beta_g \bar{m}\underline{g}, \\[2ex]
&100\sum_{k=0}^{5}\exp(-4(t-(200+2k))^2)\underline{m}(1-\bar{c}) \\
&-\gamma_c \bar{c} - k\gamma_n \underline{n}\bar{c} \geq 0 \geq 100\sum_{k=0}^{5}\exp(-4(t-(200+2k))^2)\bar{m}(1-\underline{c}) - \gamma_c \underline{c} - k\gamma_n \bar{n}\underline{c}.
\end{aligned}
\right\} \quad (29)
$$

Therefore, $(\bar{w}, \bar{n}, \bar{h}, \bar{a}, \bar{m}, \bar{f}, \bar{g}, \bar{c})$ and $(\underline{w}, \underline{n}, \underline{h}, \underline{a}, \underline{m}, \underline{f}, \underline{g}, \underline{g})$, are a pair of coupled upper and lower solutions of system (1),[22], respectively.

Thus, for any

$$(\underline{w}, \underline{n}, \underline{h}, \underline{a}, \underline{m}, \underline{f}, \underline{g}, \underline{c}) \le (w_1, n_1, h_1, a_1, m_1, g_1, c_1), \text{ and } (w_2, n_2, h_2, a_2, m_2, f_2, g_2, c_2) \le (\bar{w}, \bar{n}, \bar{h}, \bar{a}, \bar{m}, \bar{f}, \bar{g}, \bar{c})$$

we have

$$(30) \quad \left.\begin{aligned}
&\left|\alpha_w m_1(1-w_1) - \beta_w(n_1+h_1+m_1)w_1 - \gamma_w w_1\right. \\
&\left. -(\alpha_w m_2(1-w_2) - \beta_w(n_2+h_2+m_2)w_2 - \gamma_w w_2)\right| \\
&\le K(|w_1-w_2| + |n_1-n_2| + |h_1-h_2| + |a_1-a_2|), \\
&\left|\alpha_n n_1(v_{max}-v_1) - \alpha_h \mathscr{H}(w_h-w_1)n_1 + \tfrac{\alpha_h}{10}\mathscr{H}(w_1-w_h)h_1 - \gamma_n n_1 c_1\right. \\
&\left. -(\alpha_n n_2(v_{max}-v_2) - \alpha_h \mathscr{H}(w_h-w_2)n_2 + \tfrac{\alpha_h}{10}\mathscr{H}(w_2-w_h)h_2 - \gamma_n n_2 c_2)\right| \\
&\le K(|n_1-n_2| + |h_1-h_2| + |a_1-a_2| + |v_1-v_2|), \\
&\left|\alpha_h \mathscr{H}(w_h-w_1)n_1 - \tfrac{\alpha_h}{10}\mathscr{H}(w_1-w_h)h_1 - \beta_h \mathscr{H}(w_a-w_1)h_1\right. \\
&\left. -(\alpha_h \mathscr{H}(w_h-w_2)n_2 - \tfrac{\alpha_h}{10}\mathscr{H}(w_2-w_h)h_2 - \beta_h \mathscr{H}(w_a-w_2)h_2)\right| \\
&\le K(|n_1-n_2| + |h_1-h_2|), \\
&\left|\beta_h \mathscr{H}(w_a-w_1)h_1 + \gamma_n n_1 c_1 - (\beta_h \mathscr{H}(w_a-w_2)h_2 + \gamma_n n_2 c_2)\right| \\
&\le K(|n_1-n_2| + |h_1-h_2 + |c_1-c_2|), \\
&\left|\alpha_m m_1 g_1(v_{\max}-v_1) - (\alpha_m m_2 g_2(v_{\max}-v_2))\right| \\
&\le K(|m_1-m_2| + |g_1-g_2 + |v_1-v_2|), \\
&\left|-\beta_f n_1 f_1 - (-\beta_f n_2 f_2)\right| \le K(|n_1-n_2| + |f_1-f_2|), \\
&\left|\alpha_g h_1 - \beta_g m_1 g_1 - (\alpha_g h_2 - \beta_g m_2 g_2)\right| \le K(|h_1-h_2| + |m_1-m_2| + |g_1-g_2|), \\
&\left|100\sum_{k=0}^{5}\exp(-4(t-(200+2k))^2)m_1(1-c_1) - \gamma_c c_1 - k\gamma_n n_1 c_1\right. \\
&\left. -(100\sum_{k=0}^{5}\exp(-4(t-(200+2k))^2)m_2(1-c_2) - \gamma_c c_2 - k\gamma_n n_2 c_2)\right| \\
&\le K(|n_1-n_2| + |m_1-m_2| + |c_1-c_2|),
\end{aligned}\right\}$$

Defining two iteration sequences $(\bar{w}, \bar{n}, \bar{h}, \bar{a}, \bar{m}, \bar{f}, \bar{g}, \bar{c})$ and $(\underline{w}, \underline{n}, \underline{h}, \underline{a}, \underline{m}, \underline{f}, \underline{g}, \underline{c})$ for $i \geq 1$,

$$
\begin{aligned}
\bar{w}^{(i)} &= \bar{w}^{(i-1)} + (\alpha_w \underline{m}^{(i-1)}(1 - \bar{w}^{(i-1)}) - \beta_w(\underline{n}^{(i-1)} + \underline{h}^{(i-1)} + \underline{m}^{(i-1)})\bar{w}^{(i-1)} \\
&\quad - \gamma_w \bar{w}^{(i-1)})/K, \\
\bar{n}^{(i)} &= \bar{n}^{(i-1)} + (\alpha_n \bar{n}(v_{max} - (\underline{h} + \underline{a} + \bar{n} + \underline{f} + \underline{m})) - \alpha_h \mathcal{H}(w_h - \underline{w})\bar{n} \\
&\quad + \tfrac{\alpha_h}{10}\mathcal{H}(\underline{w} - w_h)h - \gamma_n \bar{n}\underline{c})/K, \\
\bar{h}^{(i)} &= \bar{h}^{(i-1)} + (\alpha_h \mathcal{H}(w_h - \bar{w}^{(i-1)})\bar{n}^{(i-1)} - \tfrac{\alpha_h}{10}\mathcal{H}(\bar{w}^{(i-1)} - w_h)\bar{h}^{(i-1)} \\
&\quad - \beta_h \mathcal{H}(w_a - \bar{w}^{(i-1)})\bar{h}^{(i-1)})/K, \\
\bar{a}^{(i)} &= \bar{a}^{(i-1)} + (\beta_h \mathcal{H}(w_a - \underline{w}^{(i-1)})\underline{h}^{(i-1)} + \gamma_n \underline{n}^{(i-1)}\underline{c}^{(i-1)})/K, \\
\bar{m}^{(i)} &= \bar{m}^{(i-1)} + (\alpha_m \bar{m}^{(i-1)}\underline{g}^{(i-1)}(v_{max} - (\underline{v}^{(i-1)})))/K, \\
\bar{f}^{(i)} &= \bar{f}^{(i-1)} + (-\beta_f \underline{n}^{(i-1)}\bar{f}^{(i-1)})/K, \\
\bar{g}^{(i)} &= \bar{g}^{(i-1)} + (\alpha_g \underline{h}^{(i-1)} - \beta_g \underline{m}^{(i-1)}\bar{g}^{(i-1)})/K, \\
\bar{c}^{(i)} &= \bar{c}^{(i-1)} + ((100\textstyle\sum_{k=0}^{5}\exp(-4(t - (200 + 2k))^2)\underline{m}^{(i-1)}(1 - \bar{c}^{(i-1)}) \\
&\quad - \gamma_c \bar{c}^{(i-1)} - k\gamma_n \underline{n}^{(i-1)}\bar{c}^{(i-1)})/K, \\
\underline{w}^{(i)} &= \underline{w}^{(i-1)} + (\alpha_w \bar{m}(1 - \underline{w}) - \beta_w(\bar{n} + \bar{h} + \bar{m})\underline{w} - \gamma_w \underline{w})/K, \\
\underline{n}^{(i)} &= \underline{n}^{(i-1)} + (\alpha_n \underline{n}^{(i-1)}(v_{max} - (\bar{h}^{(i-1)} + \bar{a}^{(i-1)} + \underline{n}^{(i-1)} + \bar{f}^{(i-1)} + \bar{m}^{(i-1)})) \\
&\quad - \alpha_h \mathcal{H}(w_h - \bar{w}^{(i-1)})\underline{n}^{(i-1)} + \tfrac{\alpha_h}{10}\mathcal{H}(\bar{w}^{(i-1)} - w_h)h - \gamma_n \underline{n}^{(i-1)}\bar{c}^{(i-1)})/K, \\
\underline{h}^{(i)} &= \underline{h}^{(i-1)} + (\alpha_h \mathcal{H}(w_h - \underline{w}^{(i-1)})\underline{n}^{(i-1)} \\
&\quad - \tfrac{\alpha_h}{10}\mathcal{H}(\underline{w}^{(i-1)} - w_h)\underline{h}^{(i-1)} - \beta_h \mathcal{H}(w_a - \underline{w}^{(i-1)})\underline{h}^{(i-1)})/K, \\
\underline{a}^{(i)} &= \underline{a}^{(i-1)} + (\beta_h \mathcal{H}(w_a - \bar{w}^{(i-1)})\bar{h}^{(i-1)} + \gamma_n \bar{n}^{(i-1)}\bar{c}^{(i-1)})/K, \\
\underline{m}^{(i)} &= \underline{m}^{(i-1)} + (\alpha_m \underline{m}^{(i-1)}\bar{g}^{(i-1)}(v_{max} - (\bar{h}^{(i-1)} + \bar{a}^{(i-1)} + \bar{n}^{(i-1)} + \bar{f}^{(i-1)} + \underline{m}^{(i-1)})), \\
\underline{f}^{(i)} &= \underline{f}^{(i-1)} + (-\beta_f \underline{n}^{(i-1)}\underline{f}^{(i-1)})/K, \\
\underline{g}^{(i)} &= \underline{g}^{(i-1)} + (\alpha_g \bar{h}^{(i-1)} - \beta_g \bar{m}^{(i-1)}\underline{g}^{(i-1)})/K, \\
\underline{c}^{(i)} &= \underline{c}^{(i-1)} + (100\textstyle\sum_{k=0}^{5}\exp(-4(t - (200 + 2k))^2)\bar{m}^{(i-1)}(1 - \underline{c}^{(i-1)}) - \gamma_c \underline{c}^{(i-1)} \\
&\quad - k\gamma_n \bar{n}^{(i-1)}\underline{c}^{(i-1)})/K.
\end{aligned}
\tag{31}
$$

where $(\bar{w}^{(0)}, \bar{n}^{(0)}, \bar{h}^{(0)}, \bar{a}^{(0)}, \bar{m}^{(0)}, \bar{f}^{(0)}, \bar{g}^{(0)}, \bar{c}^{(0)}) = (\bar{w}, \bar{n}, \bar{h}, \bar{a}, \bar{m}, \bar{f}, \bar{g}, \bar{c})$

and $(\underline{w}^{(0)}, \underline{n}^{(0)}, \underline{h}^{(0)}, \underline{a}^{(0)}, \underline{m}^{(0)}, \underline{f}^{(0)}, \underline{g}^{(0)}, \underline{c}^{(0)}) = (\underline{w}, \underline{n}, \underline{h}, \underline{a}, \underline{m}, \underline{f}, \underline{g}, \underline{c})$. Thus, for $i \geq 1$

$$
\begin{aligned}
(\underline{w}, \underline{n}, \underline{h}, \underline{a}, \underline{m}, \underline{f}, \underline{g}, \underline{c}) &\leq (\underline{w}^{(i)}, \underline{n}^{(i)}, \underline{h}^{(i)}, \underline{a}^{(i)}, \underline{m}^{(i)}, \underline{f}^{(i)}, \underline{g}^{(i)}, \underline{c}^{(i)}) \\
&\leq (\underline{w}^{(i+1)}, \underline{n}^{(i+1)}, \underline{h}^{(i+1)}, \underline{a}^{(i+1)}, \underline{m}^{(i+1)}, \underline{f}^{(i+1)}, \underline{g}^{(i+1)}, \underline{c}^{(i+1)}) \\
&\leq (\bar{w}^{(i+1)}, \bar{n}^{(i+1)}, \bar{h}^{(i+1)}, \bar{a}^{(i+1)}, \bar{m}^{(i+1)}, \bar{f}^{(i+1)}, \bar{g}^{(i+1)}, \bar{c}^{(i+1)}) \\
&\leq (\bar{w}^{(i)}, \bar{n}^{(i)}, \bar{h}^{(i)}, \bar{a}^{(i)}, \bar{m}^{(i)}, \bar{f}^{(i)}, \bar{g}^{(i)}, \bar{c}^{(i)}) \leq (\bar{w}, \bar{n}, \bar{h}, \bar{a}, \bar{m}, \bar{f}, \bar{g}, \bar{c}),
\end{aligned}
$$

and there exist $(\tilde{w}^{(0)}, \tilde{n}^{(0)}, \tilde{h}^{(0)}, \tilde{a}^{(0)}, \tilde{m}^{(0)}, \tilde{f}^{(0)}, \tilde{g}^{(0)}, \tilde{c}^{(0)}) > (0,0,0,0,0)$

and $(\hat{w}^{(0)}, \hat{n}^{(0)}, \hat{h}^{(0)},, \hat{a}^{(0)}, \hat{m}^{(0)}, \hat{f}^{(0)}, \hat{g}^{(0)}, \hat{c}^{(0)}) > (0,0,0,0,0)$ such that

$$\lim_{i \to \infty} \bar{w} = \tilde{w}, \lim_{i \to \infty} \bar{n} = \tilde{n}, \lim_{i \to \infty} \bar{h} = \tilde{h}, \lim_{i \to \infty} \bar{a} = \tilde{a}, \lim_{i \to \infty} \bar{m} = \tilde{m}, \lim_{i \to \infty} \bar{f} = \tilde{f}, \lim_{i \to \infty} \bar{g} = \tilde{g}, \lim_{i \to \infty} \bar{c} = \tilde{c}$$

and

$$\lim_{i \to \infty} \underline{w} = \hat{w}, \lim_{i \to \infty} \underline{n} = \hat{n}, \lim_{i \to \infty} \underline{h} = \hat{h}, \lim_{i \to \infty} \underline{a} = \hat{a}, \lim_{i \to \infty} \underline{m} = \hat{m}, \lim_{i \to \infty} \underline{f} = \hat{f}, \lim_{i \to \infty} \underline{g} = \hat{g}, \lim_{i \to \infty} \underline{c} = \hat{c},$$

and

$$
\begin{aligned}
&\alpha_w \hat{m}(1 - \tilde{w}) - \beta_w(\hat{n} + \hat{h} + \hat{m})\bar{w} - \gamma_w \tilde{w} = 0, \\
&\alpha_w \tilde{m}(1 - \hat{w}) - \beta_w(\tilde{n} + \tilde{h} + \tilde{m})\hat{w} - \gamma_w \hat{w} = 0,
\end{aligned}
$$

$$
\begin{aligned}
&\alpha_n \tilde{n}(v_{max} - (\hat{h} + \hat{a} + \tilde{n} + \hat{f} + \hat{m})) - \alpha_h \mathscr{H}(w_h - \hat{w})\tilde{n} + \tfrac{\alpha_h}{10}\mathscr{H}(\hat{w} - w_h)\hat{h} - \gamma_n \tilde{n}\hat{c} = 0, \\
&\alpha_n \hat{n}(v_{max} - (\tilde{h} + \tilde{a} + \tilde{n} + \tilde{f} + \tilde{m})) - \alpha_h \mathscr{H}(w_h - \tilde{w})\hat{n} + \tfrac{\alpha_h}{10}\mathscr{H}(\tilde{w} - w_h)\tilde{h} - \gamma_n \hat{n}\tilde{c} = 0,
\end{aligned}
$$

$$
\begin{aligned}
&\alpha_h \mathscr{H}(w_h - \tilde{w})\tilde{n} - \tfrac{\alpha_h}{10}\mathscr{H}(\tilde{w} - w_h)\tilde{h} - \beta_h \mathscr{H}(w_a - \tilde{w})\tilde{h} = 0 \\
&\alpha_h \mathscr{H}(w_h - \hat{w})\hat{n} - \tfrac{\alpha_h}{10}\mathscr{H}(\hat{w} - w_h)\hat{h} - \beta_h \mathscr{H}(w_a - \hat{w})\hat{h} = 0,
\end{aligned}
$$

$$
\begin{aligned}
&\beta_h \mathscr{H}(w_a - \hat{w})\hat{h} + \gamma_n \hat{n}\hat{c} = 0, \\
&\beta_h \mathscr{H}(w_a - \tilde{w})\tilde{h} + \gamma_n \tilde{n}\tilde{c} = 0,
\end{aligned}
$$

(32)

$$
\begin{aligned}
&\alpha_m \tilde{m}\hat{g}(v_{\max} - (\hat{h} + \hat{a} + \hat{n} + \hat{f} + \tilde{m})) = 0, \\
&\alpha_m \hat{m}\tilde{g}(v_{\max} - (\tilde{h} + \tilde{a} + \tilde{n} + \tilde{f} + \hat{m})),
\end{aligned}
$$

$$
\begin{aligned}
&-\beta_f \tilde{n}\tilde{f} = 0, \\
&-\beta_f \hat{n}\hat{f} = 0,
\end{aligned}
$$

$$
\begin{aligned}
&\alpha_g \hat{h} - \beta_g \hat{m}\tilde{g} = 0, \\
&\alpha_g \tilde{h} - \beta_g \tilde{m}\hat{g} = 0,
\end{aligned}
$$

$$
\begin{aligned}
&100\textstyle\sum_{k=0}^{5} \exp(-4(t - (200 + 2k))^2)\hat{m}(1 - \tilde{c}) - \gamma_c \tilde{c} - k\gamma_n \hat{n}\tilde{c} = 0, \\
&100\textstyle\sum_{k=0}^{5} \exp(-4(t - (200 + 2k))^2)\tilde{m}(1 - \hat{c}) - \gamma_c \hat{c} - k\gamma_n \tilde{n}\hat{c} = 0.
\end{aligned}
$$

Since, the equilibrium points in equation (16) is the unique semi-positive constant equilibrium of system (1), it must hold for

$$(33) \quad \begin{aligned} (\tilde{w},\tilde{n},\tilde{h},\tilde{a},\tilde{m},\tilde{f},\tilde{g},\tilde{c}) &= (\hat{w},\hat{n},\hat{h},\hat{a},\hat{m},\hat{f},\hat{g},\hat{c}) \\ &= (\frac{\alpha_w v_{\max}}{\alpha_w + \beta_w v_{\max} + \gamma_w},0,0,0,v_{\max},0,0,c^* > 0). \end{aligned}$$

Thus, by [14, 15], the solution $(\frac{\alpha_w v_{\max}}{\alpha_w + \beta_w v_{\max} + \gamma_w},0,0,0,v_{\max},0,0,c^* > 0)$ of system (1) satisfies

$$\begin{aligned} \lim_{t\to\infty} w(x,t) &= w^*, \ \lim_{t\to\infty} n(x,t) = n^*, \ \lim_{t\to\infty} h(x,t) = h^*, \ \lim_{t\to\infty} a(x,t) = a^* \ \lim_{t\to\infty} m(x,t) = m^*, \\ (34)\lim_{t\to\infty} f(x,t) &= f^*, \ \lim_{t\to\infty} g(x,t) = g^*, \ \lim_{t\to\infty} c(x,t) = c^*. \end{aligned}$$

Hence, the constant equilibrium $(\frac{\alpha_w v_{\max}}{\alpha_w + \beta_w v_{\max} + \gamma_w},0,0,0,v_{\max},0,0,c^* > 0)$ is globally asymptotically stable.

3. A construction and analysis of the numerical method

In this section, we describe the derivation of the fitted numerical method for solving the system in equation (1). We determine an approximation to the derivatives of the functions $w(t,x),n(x,t),h(x,t),a(x,t),m(x,t),f(x,t),g(x,t),c(x,t)$, with respect to the spatial variable x.

Let S_x be a positive integer. Discretize the interval $[0,x_f], x_f \in \mathbb{Z}^+$ through the points

$$0 = x_0 < x_1 < x_2 < \cdots < x_f,$$

where the step-size $\Delta x = x_{j+1} - x_j = 1/x_f, \ j = 0,1,\ldots,x_f$. Let

$$(35) \qquad W_j(t),N_j(t),H_j(t),A_j(t),M_j(t),F_j(t),G_j(t),C_j(t)$$

denote the numerical approximations of $w(t,x),n(x,t),h(x,t),a(x,t),m(x,t),f(x,t),g(x,t),c(x,t)$. Then we approximate the second order spatial derivative in the system in (1) by

$$\frac{\partial w}{\partial x^2}(t,x_j) \approx \frac{W_{j+1} - 2W_j + W_{j-1}}{\phi_w^2},$$

$$\frac{\partial}{\partial x}\left([D_n \max\{N_j - v_c, 0\} + D_m]\frac{\partial n}{\partial x} - \chi_n n \frac{\partial f}{\partial x}\right)(t,x_j)$$
$$\approx [D_n \max\{N_j - v_c, 0\} + D_m]\frac{N_{j+1} - 2N_j + N_{j-1}}{\phi_n^2} - D_x^+\left(\chi_n N_j D_x^- F_j\right),$$

(36)

$$\frac{\partial}{\partial x}\left(D_m \frac{\partial m}{\partial x} - m \chi_m \frac{\partial g}{\partial x}\right)(t,x_j) \approx \frac{M_{j+1} - 2M_j + M_{j-1}}{\phi_m^2} - D^+(M_j \chi_m D^- G_j),$$

$$\frac{\partial^2 g}{\partial x^2}(t,x_j) \approx D_x^+(D^- G_j), \ \frac{\partial^2 c}{\partial x^2}(t,x_j) \approx \frac{C_{j+1} - 2C_j + C_{j+1}}{\phi_c^2},$$

where

$$D^+(\cdot)_j = \frac{(\cdot)_{i+1} - (\cdot)_i}{\Delta x} \text{ and } D^-(\cdot)_i = \frac{(\cdot)_i - (\cdot)_{i-1}}{\Delta x},$$

and the denominator functions

$$\phi_w^2 := \frac{4}{\rho_w^2}\sinh^2\left(\frac{\rho_w \Delta x}{2}\right), \ \rho_w := \sqrt{\frac{\gamma_w}{D_w}}, \ \phi_n^2 := \frac{\tilde{D}_n \Delta x}{\chi_n}\left[\exp(\frac{\chi_n \Delta x}{\tilde{D}_n}) - 1\right],$$

$$\phi_m^2 := \frac{D_m \Delta x}{\chi_m}\left[\exp(\frac{\chi_m \Delta x}{D_m}) - 1\right], \ \phi_c^2 := \frac{4}{\rho_c^2}\sinh^2\left(\frac{\rho_c \Delta x}{2}\right), \ \rho_c := \sqrt{\frac{\gamma_c}{D_c}},$$

where $\phi_w \to \Delta x, \phi_n \to \Delta x, \phi_m \to \Delta x, \phi_c \to \Delta x$, as $\Delta x \to 0$. Let t_f be a positive integer and $j = 1/t_f$ where $0 < t < t_f$. Discretizing the time interval $[0, t_f]$ through the points

$$0 = t_0 < t_1 < \cdots < t_f,$$

where

$$t_{i+1} - t_i = \Delta t, \ i = 0, 1, \ldots, (t_f - 1).$$

We approximate the time derivative at t_i by

$$\frac{\partial w}{\partial t}(x,t_i) \approx \frac{W_{j+1}^{i+1} - W_j^i}{\psi_w}, \ \frac{\partial n}{\partial t}(x,t_i) \approx \frac{N_{j+1}^{i+1} - N_j^i}{\Delta t}, \ \frac{\partial h}{\partial t}(x,t_i) \approx \frac{H_{j+1}^{i+1} - H_j^i}{\Delta t},$$

(37)

$$\frac{\partial a}{\partial t}(x,t_i) \approx \frac{A_{j+1}^{i+1} - A_j^i}{\Delta t}, \ \frac{\partial m}{\partial t}(x,t_i) \approx \frac{M_{j+1}^{i+1} - M_j^i}{\Delta t}, \ \frac{\partial f}{\partial t}(x,t_i) \approx \frac{F_{j+1}^{i+1} - F_j^i}{\Delta t},$$

$$\frac{\partial g}{\partial t}(x,t_i) \approx \frac{G_{j+1}^{i+1} - G_j^i}{\Delta t}, \ \frac{\partial c}{\partial t}(x,t_i) \approx \frac{C_{j+1}^{i+1} - C_j^i}{\psi_c},$$

where

$$\psi_w = \psi_w(\Delta t) = (1 - \exp(-\gamma_w \Delta t))/\gamma_w, \ \psi_c = (1 - \exp(-\gamma_c \Delta t))/\gamma_c,$$

where $\psi_w \to \Delta t, \psi_c \to \Delta t$ as $\Delta t \to 0$. The denominator functions in equations (36) and (37) are used explicitly to remove the inherent stiffness in the central finite derivatives parts and can be derived by using the theory of nonstandard finite difference methods, see, e.g., [10, 16, 17] and references therein.

Combining the equation (36) for the spatial with equation (37) for time derivatives, we obtain

(38)
$$\left.\begin{array}{l}
\frac{W_{j+1}^{i+1}-W_j^i}{\psi_w} - D_w \frac{W_{j-1}^{i+1}-2W_j^{i+1}+W_{j+1}^{i+1}}{\phi_w^2} = \alpha_w M_j^i(1-W_j^i) - \beta_w(N_j^i+H_j^i+M_j^i)W_j^i \\
\quad -\gamma_w W_j^i, \\
\frac{N_{j+1}^{i+1}-N_j^i}{\Delta t} - [D_n \max\{N_j - v_c, 0\} + D_m]\frac{N_{j-1}^{i+1}-2N_j^{i+1}+N_{j+1}^{i+1}}{\phi_n^2} = \\
D^+\left(\chi_n N_j^i D^- F_j^i\right) + \alpha_n N_j^i(v_{max}-V_j^i) - \alpha_h \mathscr{H}(w_h - W_j^i)N_j^i + \frac{\alpha_h}{10}\mathscr{H}(W_j^i - w_h)H_j^i \\
\quad -\gamma_n N_j^i C_j^i, \\
\frac{H_{j+1}^{i+1}-H_j^i}{\Delta t} = \alpha_h \mathscr{H}(w_h - W_j^i)N_j^i - \frac{\alpha_h}{10}\mathscr{H}(W_i^i - w_h)H_j^i - \beta_h \mathscr{H}(w_a - W_j^i)H_j^i, \\
\frac{A_j^{i+1}-A_j^i}{\Delta t} = \beta_h \mathscr{H}(w_a - W_j^i)H_j^i + \gamma_n N_j^i C_j^i, \\
\frac{M_{j+1}^{i+1}-M_j^i}{\Delta t} - D_m \frac{M_{j-1}^{i+1}-2M_j^{i+1}+M_{j+1}^{i+1}}{\phi_m^2} = D^+(M_j^i \chi_m D^- G_j^i) + \alpha_m M_j^i G_j^i(v_{max}-V_j^i), \\
\frac{F_{j+1}^{i+1}-F_j^i}{\Delta t} = -\beta_f N_j^i F_j^i, \\
\frac{G_{j+1}^{i+1}-G_j^i}{\Delta t} - D_g \frac{G_{j-1}^{i+1}-2G_j^{i+1}+G_{j+1}^{i+1}}{(\Delta x)^2} = \alpha_g H_j^i - \beta_g M_j^i G_j^i, \\
\frac{C_{j+1}^{i+1}-C_j^i}{\psi_c} - D_c \frac{C_{j-1}^{i+1}-2C_j^{i+1}+C_{j+1}^{i+1}}{\phi_c^2} = 100\sum_{k=0}^5 \exp(-4(t_k - (200+2k))^2)M_j^i(1-C_j^i) \\
\quad -\gamma_c C_j^i - k\gamma_n N_j^i C_j^i, \\
W_1^i = W_{-1}^n, N_1^i = N_{-1}^i, H_1^i = H_{-1}^i, A_1^i = A_{-1}^i, M_1^i = M_{-1}^i, F_1^i = F_{-1}^i, G_1^i = G_{-1}^i, \\
C_1^i = C_{-1}^i, \\
W_{x_f}^i = W_{x_f-1}^i, N_{x_f}^i = N_{x_f-1}^i, H_{x_f}^i = H_{x_f-1}^i, A_{x_f}^i = A_{x_f-1}^i, M_{x_f}^i = M_{x_f-1}^i, \\
F_{x_f}^i = F_{x_f-1}^i, G_{x_f}^i = G_{x_f-1}^i, C_{x_f}^i = C_{x_f-1}^i, \\
W_j^0 = 1.0, N_j^0 = 0.93\exp(-200x_j^2), H_j^0 = A_j^0 = 0.0, M_j^0 = 0.01, \\
F_j^0 = 1 - N_j^0 - M_j^0 - 0.05, G_j^0 = 0.0, C_j^0 \in [0,1].
\end{array}\right\}$$

) We refer to the scheme in (38) as a semi-fitted operator finite difference numerical method (FOFDM), whereas when all the denominator functions in (36) and (37) are replaced with the uniform step sizes, the scheme becomes standard finite difference method (SFDM).

Let

$$\mathscr{L}_w w \equiv \frac{\partial w}{\partial t}(x,t) - D_w \frac{\partial^2 w}{\partial x^2},$$

$$\mathscr{L}_n n \equiv \frac{\partial n}{\partial t}(x,t) - \frac{\partial}{\partial x}\left((D_n \max\{n - v_c, 0\} + D_m)\frac{\partial n}{\partial x} - \chi_n n \frac{\partial f}{\partial x} \right),$$

$$\mathscr{L}_h h \equiv \frac{\partial h}{\partial t}(x,t),$$

$$\mathscr{L}_a a \equiv \frac{\partial a}{\partial t}(x,t),$$

$$\mathscr{L}_m m \equiv \frac{\partial m}{\partial t}(x,t) - \frac{\partial}{\partial x}\left(D_m \frac{\partial m}{\partial x} - m\chi_m \frac{\partial g}{\partial x} \right),$$

$$\mathscr{L}_f f \equiv \frac{\partial f}{\partial t}(x,t),$$

$$\mathscr{L}_g g \equiv \frac{\partial g}{\partial t}(x,t) - D_g \frac{\partial^2 g}{\partial x^2},$$

$$\mathscr{L}_c c \equiv \frac{\partial c}{\partial t}(x,t) - D_c \frac{\partial^2 c}{\partial x^2},$$

and denoting the piecewise approximations of

$$w(x_j,t_i), n(x_j,t_i), h(x_j,t_i), a(x_j,t_i), m(x_j,t_i), f(x_j,t_i), g(x_j,t_i), c(x_j,t_i)$$

in the interval $[x_j, t_i]$ with $w_j^i, n_j^i, h_j^i, a_j^i, m_j^i, f_j^i, g_j^i, c_j^i$, then we let

$$\mathscr{F}_w \equiv \alpha_w m_j^i (1 - w_j^i) - \beta_w (n_j^i + h_j^i + m_j^i) w_j^i - \gamma_w w_j^i,$$

$$\mathscr{F}_n \equiv \alpha_n n_j^i (v_{max} - v_j^i) - \alpha_h \mathscr{H}(w_h - w_j^i) n_j^i + \frac{\alpha_h}{10}\mathscr{H}(w_j^i - w_h) h - \gamma_n n_j^i c_j^i,$$

$$\mathscr{F}_h \equiv \alpha_h \mathscr{H}(w_h - w_j^i) n_j^i - \frac{\alpha_h}{10}\mathscr{H}(w_j^i - w_h) h_j^i - \beta_h \mathscr{H}(w_a - w_j^i) h_j^i,$$

$$\mathscr{F}_a \equiv \beta_h \mathscr{H}(w_a - w_j^i) h_j^i + \gamma_n n_j^i c_j^i,$$

$$\mathscr{F}_m \equiv \alpha_m m_j^i g_j^i (v_{max} - v_j^i),$$

$$\mathscr{F}_f \equiv -\beta_f n_j^i f_j^i,$$

$$\mathscr{F}_g \equiv \alpha_g h_j^i - \beta_g m_j^i g_j^i,$$

$$\mathscr{F}_c \equiv 100 \sum_{k=0}^{5} \exp(-4(t - (200 + 2k))^2) m_j^i (1 - c_j^i) - \gamma_c c_j^i - k\gamma_n n_j^i c_j^i.$$

Thus, in view of the FOFDM, we see that the local truncation errors $(\varsigma_w, \varsigma_n, \varsigma_h, \varsigma_a, \varsigma_m, \varsigma_f, \varsigma_g, \varsigma_c)$ are given

by

$$
(39) \qquad
\left.
\begin{aligned}
(\varsigma_w)^i_j &= (\mathscr{L}_w w)^i_j - (\mathscr{F}_w)^i_j = (\mathscr{A}_w(w-W))^i_j, \\
(\varsigma_n)^i_j &= (\mathscr{L}_n)^i_j - (\mathscr{F}_n)^i_j = (\mathscr{A}_n(n-N))^i_j, \\
(\varsigma_h)^i_j &= (\mathscr{L}_h)^i_j - (\mathscr{F}_h)^i_j = (h-H)^i_j, \\
(\varsigma_a)^i_j &= (\mathscr{L}_a a)^i_j - (\mathscr{F}_a)^i_j = (a-A)^i_j, \\
(\varsigma_m)^i_j &= (\mathscr{L}_m)^i_j - (\mathscr{F}_m)^i_j = (\mathscr{A}_m(m-M))^i_j, \\
(\varsigma_f)^i_j &= (\mathscr{L}_f)^i_j - (\mathscr{F}_f)^i_j = (\mathscr{A}_f(f-F))^i_j, \\
(\varsigma_g)^i_j &= (\mathscr{L}_g)^i_j - (\mathscr{F}_g)^i_j = (\mathscr{A}_g(g-G))^i_j, \\
(\varsigma_c)^i_j &= (\mathscr{L}_c)^i_j - (\mathscr{F}_c)^i_j = (\mathscr{A}_c(c-C))^i_j,
\end{aligned}
\right\}
$$

where

$$
\begin{aligned}
\mathscr{A}_w &= \mathrm{Tri}\left(-\frac{D_w}{\phi_w^2}, \frac{1}{\psi_w} + \frac{D_w}{\phi_w^2}, -\frac{D_w}{\phi_w^2}\right), \quad
\mathscr{A}_n = \mathrm{Tri}\left(-\frac{\tilde{D}_n}{\phi_n^2}, \frac{1}{\Delta t} + \frac{\tilde{D}_n}{\phi_n^2}, -\frac{\tilde{D}_n}{\phi_n^2}\right), \\
\mathscr{A}_m &= \mathrm{Tri}\left(-\frac{D_m}{\phi_n^2}, \frac{1}{\Delta t} + \frac{D_m}{\phi_m^2}, -\frac{D_m}{\phi_m^2}\right), \quad
\mathscr{A}_g = \mathrm{Tri}\left(-\frac{D_g}{(\Delta x)^2}, \frac{1}{\Delta t} + \frac{D_g}{(\Delta x)^2}, -\frac{D_g}{(\Delta x)^2}\right), \\
\mathscr{A}_c &= \mathrm{Tri}\left(-\frac{D_c}{\phi_c^2}, \frac{1}{\psi_c} + \frac{D_c}{\phi_c^2}, -\frac{D_c}{\phi_c^2}\right).
\end{aligned}
$$

Thus,

$$
(40) \qquad
\left.
\begin{aligned}
&\max_{1\le i\le S_t, 1\le j\le S_x} |w^i_j - W^i_j| \le ||(\mathscr{A}_w)^{-1}|| \max_{1\le i\le S_t, 1\le j\le S_x} |(\varsigma_w)^i_j|, \\[2ex]
&\max_{1\le i\le S_t, 1\le j\le S_x} |n^i_j - N^i_j| \le ||(\mathscr{A}_n)^{-1}|| \max_{1\le i\le S_t, 1\le j\le S_x} |(\varsigma_n)^i_j|, \\[2ex]
&\max_{1\le i\le S_t, 1\le j\le S_x} |h^i_j - H^i_j| \le \max_{1\le i\le S_t, 1\le j\le S_x} |(\varsigma_h)^i_j|, \\[2ex]
&\max_{1\le i\le S_t, 1\le j\le S_x} |a^i_j - A^i_j| \le \max_{1\le i\le S_t, 1\le j\le S_x} |(\varsigma_a)^i_j|, \\[2ex]
&\max_{1\le i\le S_t, 1\le j\le S_x} |m^i_j - M^i_j| \le ||(\mathscr{A}_m)^{-1}|| \max_{1\le i\le S_t, 1\le j\le S_x} |(\varsigma_m)^i_j|, \\[2ex]
&\max_{1\le i\le S_t, 1\le j\le S_x} |f^i_j - F^i_j| \le \max_{1\le i\le S_t, 1\le j\le S_x} |(\varsigma_f)^i_j|, \\[2ex]
&\max_{1\le i\le S_t, 1\le j\le S_x} |g^i_j - G^i_j| \le ||(\mathscr{A}_g)^{-1}|| \max_{1\le i\le S_t, 1\le j\le S_x} |(\varsigma_g)^i_j|, \\[2ex]
&\max_{1\le i\le S_t, 1\le j\le S_x} |c^i_j - C^i_j| \le ||(\mathscr{A}_c)^{-1}|| \max_{1\le i\le S_t, 1\le j\le S_x} |(\varsigma_c)^i_j|,
\end{aligned}
\right\}
$$

where

$$(41) \quad
\begin{cases}
\max_{1\leq i-1\leq S_t,1\leq j\leq S_x-1}|(\varsigma_w)^i_j| \leq \frac{\Delta t}{2}|w_{tt}(\zeta)| + D_w\frac{(\Delta x)^2}{12}|w_{xxxx}(\xi)|, \\[4pt]
\max_{1\leq i-1\leq S_t,1\leq j\leq S_x-1}|(\varsigma_n)^i_j| \leq \frac{\Delta t}{2}|n_{tt}(\zeta)| \\[4pt]
\qquad\qquad\qquad\qquad + [D_n\max\{N_j-v_c,0\}+D_m]\frac{(\Delta x)^2}{12}|n_{xxxx}(\xi)|, \\[4pt]
\max_{1\leq i-1\leq S_t,1\leq j\leq S_x-1}|(\varsigma_h)^i_j| \leq \frac{\Delta t}{2}|h_{tt}(\zeta)|, \\[4pt]
\max_{1\leq i-1\leq S_t,1\leq j\leq S_x-1}|(\varsigma_a)^i_j| \leq \frac{\Delta t}{2}|a_{tt}(\zeta)|, \\[4pt]
\max_{1\leq i-1\leq S_t,1\leq j\leq S_x-1}|(\varsigma_m)^i_j| \leq \frac{\Delta t}{2}|m_{tt}(\zeta)| + D_m\frac{(\Delta x)^2}{12}|m_{xxxx}(\xi)|, \\[4pt]
\max_{1\leq i-1\leq S_t,1\leq j\leq S_x-1}|(\varsigma_f)^i_j| \leq \frac{\Delta t}{2}|f_{tt}(\zeta)|, \\[4pt]
\max_{1\leq i-1\leq S_t,1\leq j\leq S_x-1}|(\varsigma_g)^i_j| \leq \frac{\Delta t}{2}|g_{tt}(\zeta)| + D_g\frac{(\Delta x)^2}{12}|g_{xxxx}(\xi)|, \\[4pt]
\max_{1\leq i-1\leq S_t,1\leq j\leq S_x-1}|(\varsigma_c)^i_j| \leq \frac{\Delta t}{2}|c_{tt}(\zeta)| + D_c\frac{(\Delta x)^2}{12}|c_{xxxx}(\xi)|,
\end{cases}$$

for $t_{i-1} \leq \zeta \leq t_{i+1}$, $x_{j-1} \leq \xi \leq x_{j+1}$ and by [18] we have

$$(42) \quad
\begin{aligned}
||(\mathscr{A}_w)^{-1}|| &\leq \Xi_w, ||(\mathscr{A}_n)^{-1}|| \leq \Xi_n, ||(\mathscr{A}_m)^{-1}|| \leq \Xi_m, \\
||(\mathscr{A}_g)^{-1}|| &\leq \Xi_g . ||(\mathscr{A}_c)^{-1}|| \leq \Xi_c.
\end{aligned}$$

Using (41) and (42) in (40), we obtain

$$(43) \quad
\begin{cases}
\max_{1\leq i\leq S_t,1\leq j\leq S_x}|w^i_j - W^i_j| \leq \Xi_w[\frac{\Delta t}{2}|w_{tt}(\zeta)| + D_w\frac{(\Delta x)^2}{12}|w_{xxxx}(\xi)|], \\[4pt]
\max_{1\leq i\leq S_t,1\leq j\leq S_x}|n^i_j - N^i_j| \leq \Xi_n[\frac{\Delta t}{2}|(n_{tt}(\zeta)| \\[4pt]
\qquad\qquad [D_n\max\{N_j-v_c,0\}+D_m]\frac{(\Delta x)^2}{12}|n_{xxxx}(\xi)|], \\[4pt]
\max_{1\leq i\leq S_t,1\leq j\leq S_x}|h^i_j - H^i_j| \leq \frac{\Delta t}{2}|h_{tt}(\zeta)|, \\[4pt]
\max_{1\leq i\leq S_t,1\leq j\leq S_x}|a^i_j - A^i_j| \leq \frac{\Delta t}{2}|a_{tt}(\zeta)|, \\[4pt]
\max_{1\leq i\leq S_t,1\leq j\leq S_x}|m^i_j - M^i_j| \leq \Xi_m[\frac{\Delta t}{2}|m_{tt}(\zeta)| + D_m\frac{(\Delta x)^2}{12}|m_{xxxx}(\xi)|], \\[4pt]
\max_{1\leq i\leq S_t,1\leq j\leq S_x}|f^i_j - F^i_j| \leq \frac{\Delta t}{2}|f_{tt}(\zeta)|, \\[4pt]
\max_{1\leq i\leq S_t,1\leq j\leq S_x}|g^i_j - G^i_j| \leq \Xi_g[\frac{\Delta t}{2}|g_{tt}(\zeta)| + D_g\frac{(\Delta x)^2}{12}|g_{xxxx}(\xi)|], \\[4pt]
\max_{1\leq i\leq S_t,1\leq j\leq S_x}|c^i_j - C^i_j| \leq \Xi_c[\frac{\Delta t}{2}|c_{tt}(\zeta)| + D_c\frac{(\Delta x)^2}{12}|c_{xxxx}(\xi)|].
\end{cases}$$

Hence, we obtain the following results. **Theorem 3.1.** *Let*

$$\mathscr{F}_w(x,t), \mathscr{F}_n(x,t), \mathscr{F}_h(x,t), \mathscr{F}_a(x,t), \mathscr{F}_m(x,t), \mathscr{F}_f(x,t), \mathscr{F}_g(x,t), \mathscr{F}_c(x,t),$$

be sufficiently smooth functions so that $w(x,t), n(x,t), h(x,t), a(x,t), m(x,t), f(x,t), g(x,t), c(x,t) \in C^{1,2}([1,S_x] \times [1,S_t])$. *Let* $(W^i_j, N^i_j, H^i_j, A^i_j, M^i_j, F^i_j, G^i_j, C^i_j)$, $j = 1,2,\dots S_x, i = 1,2,\dots S_t$ *be the approximate solutions to* *(1), obtained using the semi-FOFDM with* $W^0_j = w^0_j, N^0_j = n^0_j, H^0_j = h^0_j, A^0_j = a^0_j, M^0_j = m^0_j, F^0_j = f^0_j, G^0_j =$

$g_j^0, c_j^0 = c_j^0$. *Then there exists* $\Xi_w, \Xi_n, \Xi_h, \Xi_a, \Xi_m, \Xi_f, \Xi_g, \Xi_c$ *independent of the step sizes* Δt *and* Δx *such that*

$$(44) \quad \left. \begin{aligned}
&\max_{1 \leq i \leq S_t, 1 \leq j \leq S_x} |w_j^i - W_j^i| \leq \Xi_w [\tfrac{\Delta t}{2} |w_{tt}(\zeta)| + D_w \tfrac{(\Delta x)^2}{12} |w_{xxxx}(\xi)|], \\
&\max_{1 \leq i \leq S_t, 1 \leq j \leq S_x} |n_j^i - N_j^i| \leq \Xi_n [\tfrac{\Delta t}{2} |n_{tt}(\zeta)| \\
&\hspace{6em} + [D_n \max\{N_j - v_c, 0\} + D_m] \tfrac{(\Delta x)^2}{12} |n_{xxxx}(\xi)|], \\
&\max_{1 \leq i \leq S_t, 1 \leq j \leq S_x} |h_j^i - H_j^i| \leq \tfrac{\Delta t}{2} |h_{tt}(\zeta)|, \\
&\max_{1 \leq i \leq S_t, 1 \leq j \leq S_x} |a_j^i - A_j^i| \leq \tfrac{\Delta t}{2} |a_{tt}(\zeta)|, \\
&\max_{1 \leq i \leq S_t, 1 \leq j \leq S_x} |m_j^i - M_j^i| \leq \Xi_m [\tfrac{\Delta t}{2} |m_{tt}(\zeta)| + D_m \tfrac{(\Delta x)^2}{12} |m_{xxxx}(\xi)|], \\
&\max_{1 \leq i \leq S_t, 1 \leq j \leq S_x} |f_j^i - F_j^i| \leq \tfrac{\Delta t}{2} |f_{tt}(\zeta)|, \\
&\max_{1 \leq i \leq S_t, 1 \leq j \leq S_x} |g_j^i - G_j^i| \leq \Xi_g [\tfrac{\Delta t}{2} |g_{tt}(\zeta)| + D_g \tfrac{(\Delta x)^2}{12} |g_{xxxx}(\xi)|], \\
&\max_{1 \leq i \leq S_t, 1 \leq j \leq S_x} |c_j^i - C_j^i| \leq \Xi_c [\tfrac{\Delta t}{2} |c_{tt}(\zeta)| + D_c \tfrac{(\Delta x)^2}{12} |c_{xxxx}(\xi)|].
\end{aligned} \right\}$$

4. Numerical results and discussions

Since the stability conditions in equations (21) and (22) are partially related to the core behaviors of tumor cells as mentioned in [6, *page 526*], then based on these conditions, it suffices to demonstrate the robustness of our numerical method through $t = 5$ and $t = 10$ for all the models. Thus, setting $t = 5$, $x_f = x_t = 1$ (for 50 number of sub-intervals) and using the parameters in Table 1, we present the baseline model's numerical results for $t = 5$ in Figure 1 and for $t = 10$, the numerical results is presented in Figure 2. For the anti-angiogenic chemotherapy model's at $t = 5$, the numerical results are presented in Figure 3 and for $t = 10$ are in Figure 4. Numerical results for anti-cytotoxic chemotherapy at $t = 5$ are present in Figure 5, whereas for $t = 10$ are presented in Figure 6.

Baseline model: At $t = 5$, we see that the oxygen concentration (w) is at its maximum level but as time passes we see a sharp decrease of the oxygen concentration (w), while the normoxic cells (n) start of slightly very low before they rise sharply to their highest point just before they start to decrease sharply. Despite the sharp decrease of the normoxic cells (n), we also see hypoxic cells (h) emerging slowly towards its highest peak just before its turning point, hypoxia early behaviors are slightly similar to the apoptic cells' (a) behaviors expect that apoptic cells (a) emerges slightly after the hypoxic cells has already started establishing themselves in a host. Moreover the apoptic cells (a) have no turning point as we see for the hypoxic cells profile(h). The endothelial cells (m) start off at higher peak, with a slight increase which is capped by the sudden decrease. Similar behavior can also be seen on the extra-cellular

matrix (f) profile. The angiogenic cells (m) have the same behaviors as the apaoptic cells (a). At $t = 10$ in Figure 2, we see that the above-mentioned behaviors are taking place at a later stage than at $t = 5$.

Anti-angiogenic chemotherapy model: For this model we only see a different profile for the oxygen concentration. Therefore, we are only discussing the profile of the oxygen concentration, because others profiles are the same as in the case of the baseline model. Thus, we see that the oxygen concentration starts at its highest point just before it starts to decrease sharply to its low point. The low concentration of oxygen is followed by the gradual increase in the concentration of the oxygen. At $t = 10$ in Figure 4, we see that the above-mentioned behaviors are taking place at a later stage than at $t = 5$.

Cytotoxic chemotherapy model: All the figures are similar to the case of the anti-angiogenic chemotherapy model, except that of the additional drug, the cytotoxic cells. The profile of the cytotoxic cells starts of very higher, but as time passes, we see a very sharp decreasing profile of the cells, and at $t = 10$ in Figure 6, the above-mentioned behaviors are taking place at a later stage than at $t = 5$.

3. Conclusion

In this paper, we examined the baseline, anti-angiogenic chemotherapy and cytotoxic chemotherapy models. The lack of mathematical expositions of these model in the literature, as well as in [6] motivated us to analyse these models. Thus, our mathematical analysis has revealed that the structural phenomena of these models are mainly contained within the baseline model. Thus, as suggested by the stability conditions of the models, our numerical results present an interesting features which goes hand in hand with the derived stability conditions. In view of our mathematical analysis, we see that, there is no condition on how to stabilize the apoptic and angeogenic growth. Thus, we see in all the figures that the apoptic and angeogenic cells grows unabated or unarltered by any of the proposed treatment. This has made it difficult for us to determine the parameter space, which can be used by the experimentalists with regard to which parameters influence the tumor behavior most. It is this evidence, which we believe that our numerical method succeeded in presenting the desire outcomes of our paper. Thus, though the models considered are not solvable analytically, but our numerical findings are in good agreement with the stability hypotheses. Thus, we believe that in this paper, we have lay the ground for further investigation into the model proposed by Hinow et al. [6].

Conflict of Interests

The authors declare that there is no conflict of interests.

REFERENCES

[1] R.L. Burden and J.D. Faires, Numerical Analysis Brooks/Cole, USA, 2011.

[2] J.C. Butcher, Implicit RungeKutta processes, Math. Comput., 18(85) (1964), 50-64.

[3] C. Cherubini, A. Gizzi, M. Bertolaso, V. Tambone, and S. Filippi, A Bistable Field Model of Cancer Dynamics, Commun. Comput. Phys. 11(1) (2012), 1-18.

[4] V. Cristini, X. Li, J.S. Lowengrub and S.M. Wise, Nonlinear simulations of solid tumor growth using a mixture model: invasion and branching, J. Math. Biol. 58(4-5) (2008), 723-763.

[5] S.O. Fatunla, Numerical Methods for IVPs in Ordinary Differential Equations, Academic Press Inc. Harcourt Brace Jovanovich Publishers, New York, 1988.

[6] P. Hinow, P. Gerlee, L.J. McCawley, V. Quaranta, M. Ciobanu, S. Wang, J.M. Graham, B.P. Ayati, K.R. Swanson, J. Claridge, M. Loveless and A.R.A. Anderson, A spatial model of tumor-host interaction: application of chemotherapy, Math. Biosci. Eng. 6(3) (2009), 521-546.

[7] A. Jemal, R. Siegel and E. Ward E, Cancer statistics, A Cancer Journal for Clinicians 58 (2008), 71-96.

[8] D.W. Jordan and P. Smith, Nonlinear Ordinary Differential Equations, Clarendon Press, Oxford, 1987.

[9] V. Mendez, S. Fedotov and W. Horsthemke, Reaction-Transport Systems: Mesoscopic Foundations, Fronts, and Spatial Instabilities, Springer, Berlin Heidelberg, 2010.

[10] R.E. Mickens, Nonstandard Finite Difference Models of Differential Equations, World Scientific, Singapore, 1994.

[11] J.D. Murray, Mathematical Biology I: An Introduction, Springer, New York, 2002.

[12] J.D. Murray, Mathematical Biology II: Spatial Models and Biomedical Applications, Springer, Berlin, 2003.

[13] "II Neoplasms", World Health Organization. Retrieved 19 June 2014.

[14] C.V. Pao, Nonlinear Parabolic and Elliptic Equations, Plenum, New York, 1996.

[15] C.V. Pao, Convergence of solutions of reaction-diffusion systems with time delays, Nonlinear Anal., Theory Methods Appl. 48 (2002), 349-362.

[16] K.C. Patidar, On the use of non-standard finite difference methods, J. Difference Equ. Appl. 11 (2005), 735-758.

[17] K.C. Patidar, Nonstandard finite difference methods: recent trends and further developments, J. Difference Equ. Appl. 22(6) (2016), 817-849.

[18] P.N. Shivakumar and K. Ji, Upper and lower bounds for inverse elements of finite and infinite tridiagonal matrices, Linear Algebra Appl. 247 (1996), 297-316.

[19] Y. Tao and M. Winkler, A Chemotaxis-Haptotaxis Model: The Roles of Nonlinear Diffusion and Logistic Source, SIAM J. Math. Anal. 43(2) (2011), 685-704.

[20] N.H. Tuan, V. Van Au, V.A. Khoa and D. Lesnic, Identification of the population density of a species model with nonlocal diffusion and nonlinear reaction, Inverse Probl. 33(5) (2017), Article ID 055019.

[21] L.N. Trefethen, Finite Difference and Spectral Methods for Ordinary and Partial Differential Equations, Upson Hall Cornell University Ithaca, New York, 1996.

[22] Q.X. Ye and Z.Y. Li, Introduction to Reaction-Diffusion Equations, Science Press, Beijing, China, 1990.

[23] V. Vavourakis, P.A. Wijeratne, R. Shipley, M. Loizidou, T. Stylianopoulos and D.J. Hawkes, A Validated Multiscale In-Silico Model for Mechano-sensitive tumor Angiogenesis and Growth, Plos Comput. Biol. 13 (2017), Article ID e1005259.

TABLE 1. Parameter values

$D_w = 0.58$	$\alpha_w = 1.00$	$\beta_w = 0.57$	$\gamma_w = 0.025$
$\beta_h = .32$	$w_h = 0.05$	$w_a = 0.03$	$\beta_f = 0.50$
$D_n = 5.7600 \times 10^{-5}$	$v_c = 0.8$	$\chi_n = 1.4 \times 10^{-4}$	$D_m = 5.7600 \times 10^{-05}$
$D_g = 0.02$	$\chi_m = 2.1 \times 10^{-6}$	$\alpha_m = 0.07$	$\alpha_g = 10.00$
$\beta_g = 10.00$	$D_c = 0.5$	$v_{\max} = 3$	$\alpha_h = 1.60$
$\alpha_n = \log(2)$	$\gamma_c = .21$	$k = 10.5$	$\gamma_n = 0.7$
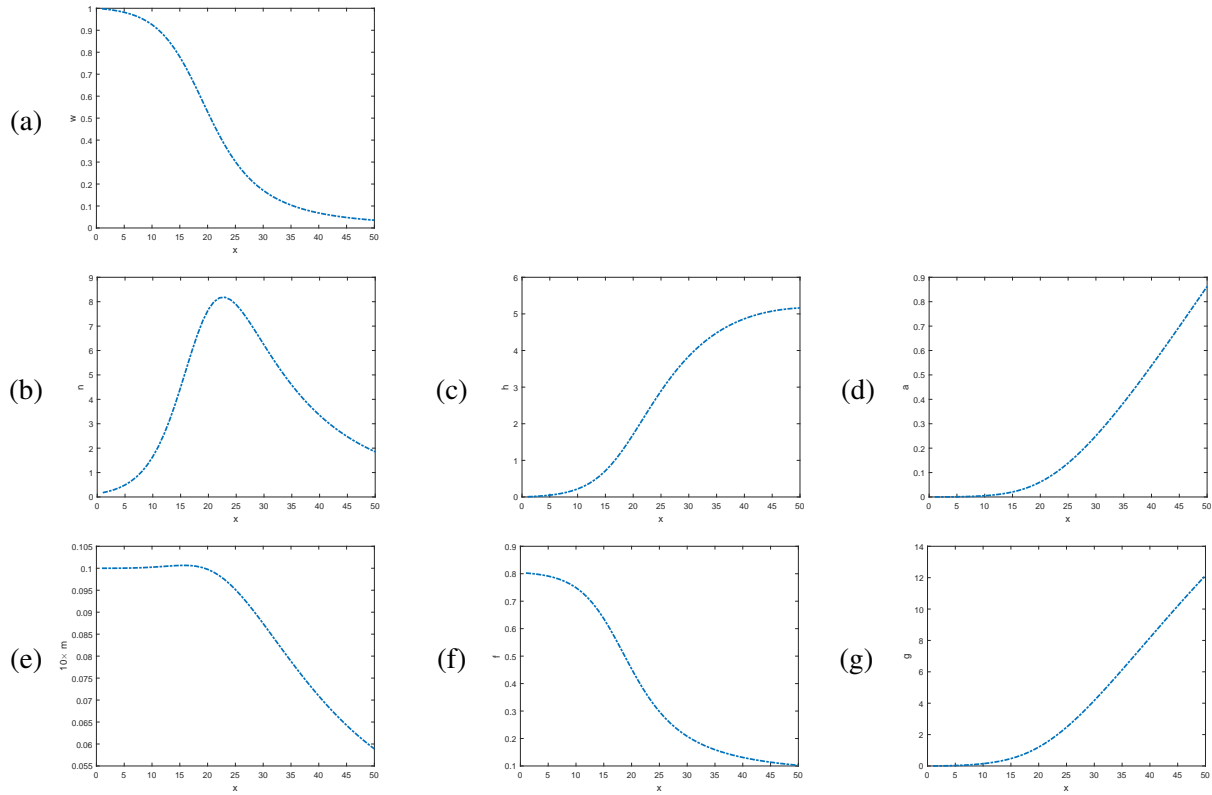
FIGURE 1. Numerical solution of the baseline model at $t = 5$, presenting the spatial distributions of: (a) oxygen, (b) normoxic, (c) hypoxic, (d) apoptic, (e) endothelial, (f) extracellular matrix and (g) angiogenic cells. Parameter values are as given in Table 1
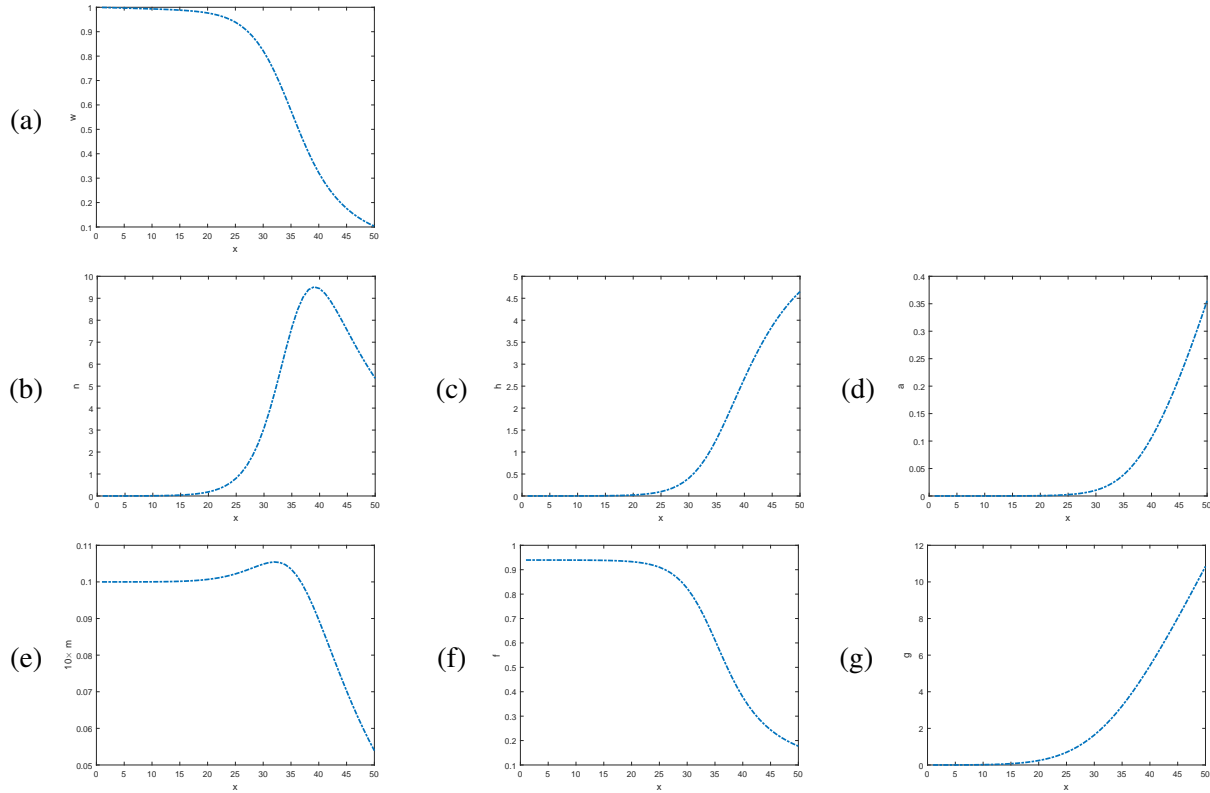
FIGURE 2. Numerical solution of the baseline model at $t = 10$, presenting the spatial distributions of: (a) oxygen, (b) normoxic, (c) hypoxic, (d) apoptic, (e) endothelial, (f) extracellular matrix and (g) angiogenic cells. Parameter values are as given in Table 1
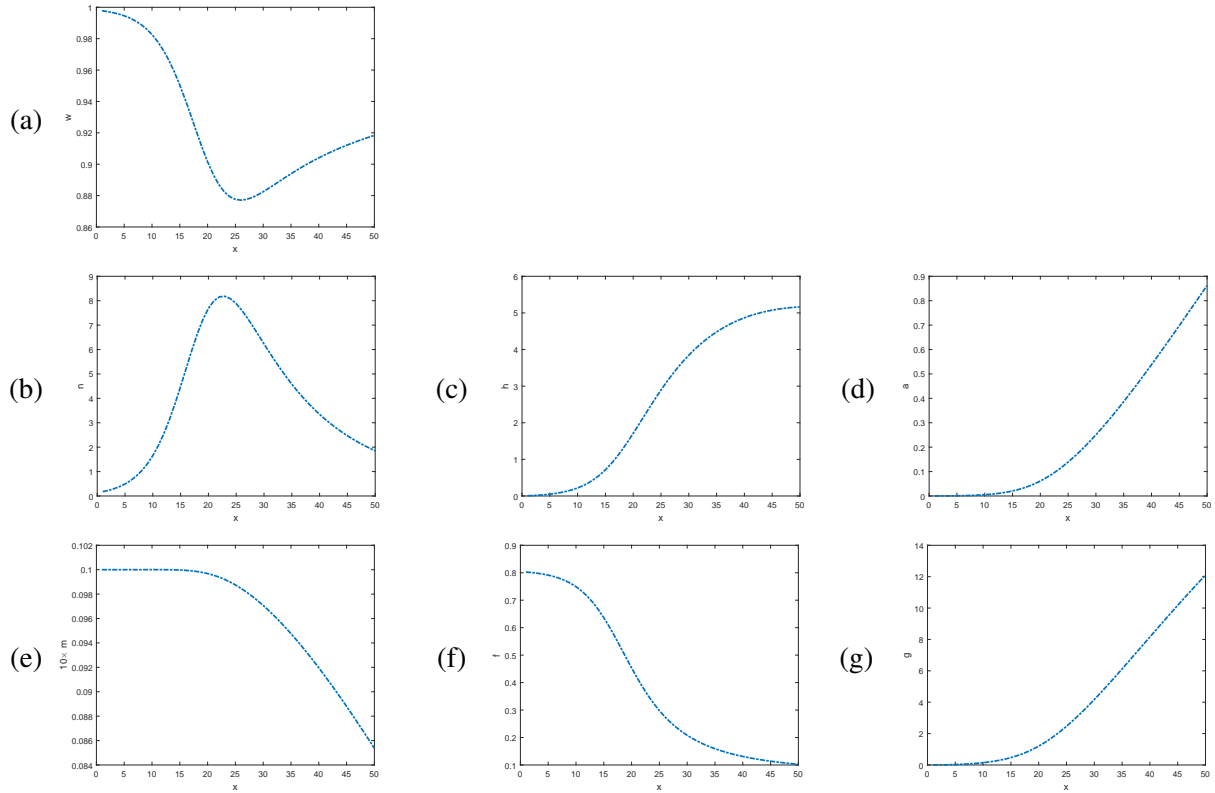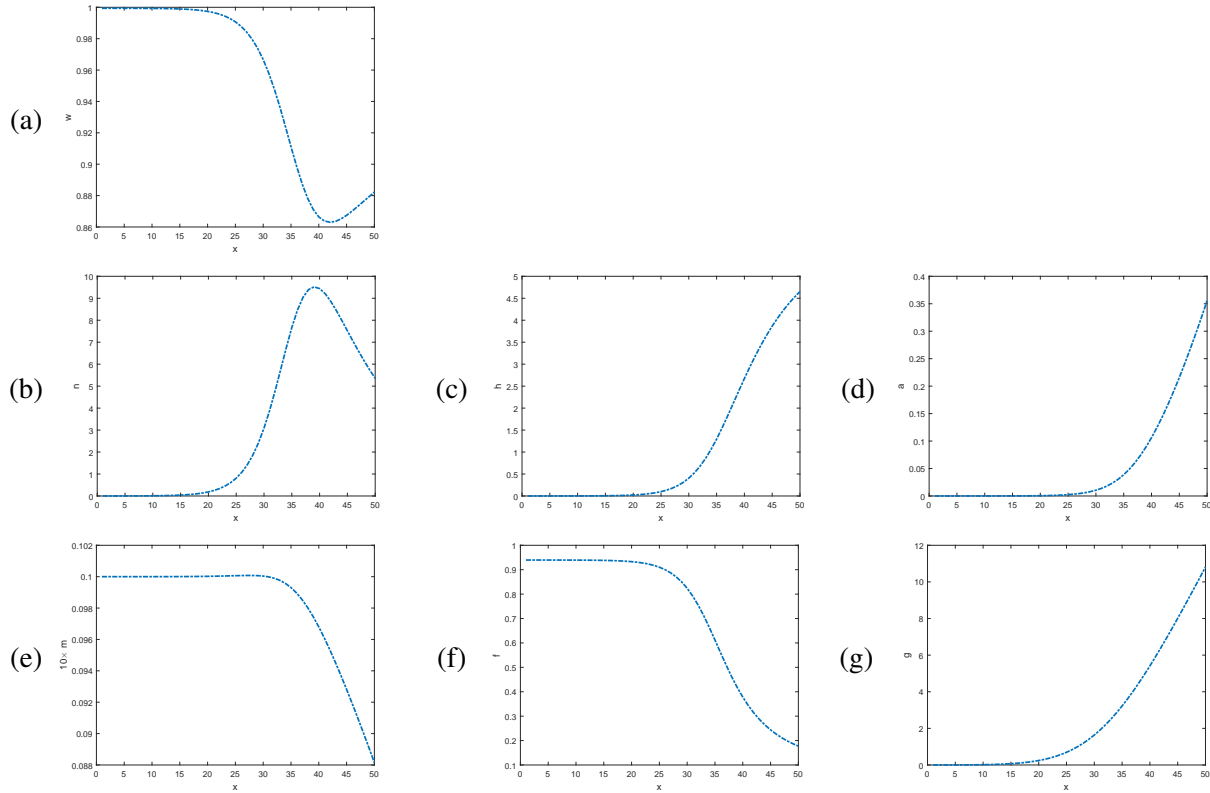
FIGURE 3. Numerical solution of anti-angiogenic chemotherapy model at $t = 5$ presenting the spatial distributions of: (a) oxygen, (b) normoxic, (c) hypoxic, (d) apoptic, (e) endothelial, (f) extracellular matrix and (g) angiogenic cells. Parameter values are as given in Table 1.

FIGURE 4. Numerical solution of anti-angiogenic chemotherapy model at $t = 10$ presenting the spatial distributions of: (a) oxygen, (b) normoxic, (c) hypoxic, (d) apoptic, (e) endothelial, (f) extracellular matrix and (g) angiogenic cells. Parameter values are as given in Table 1.
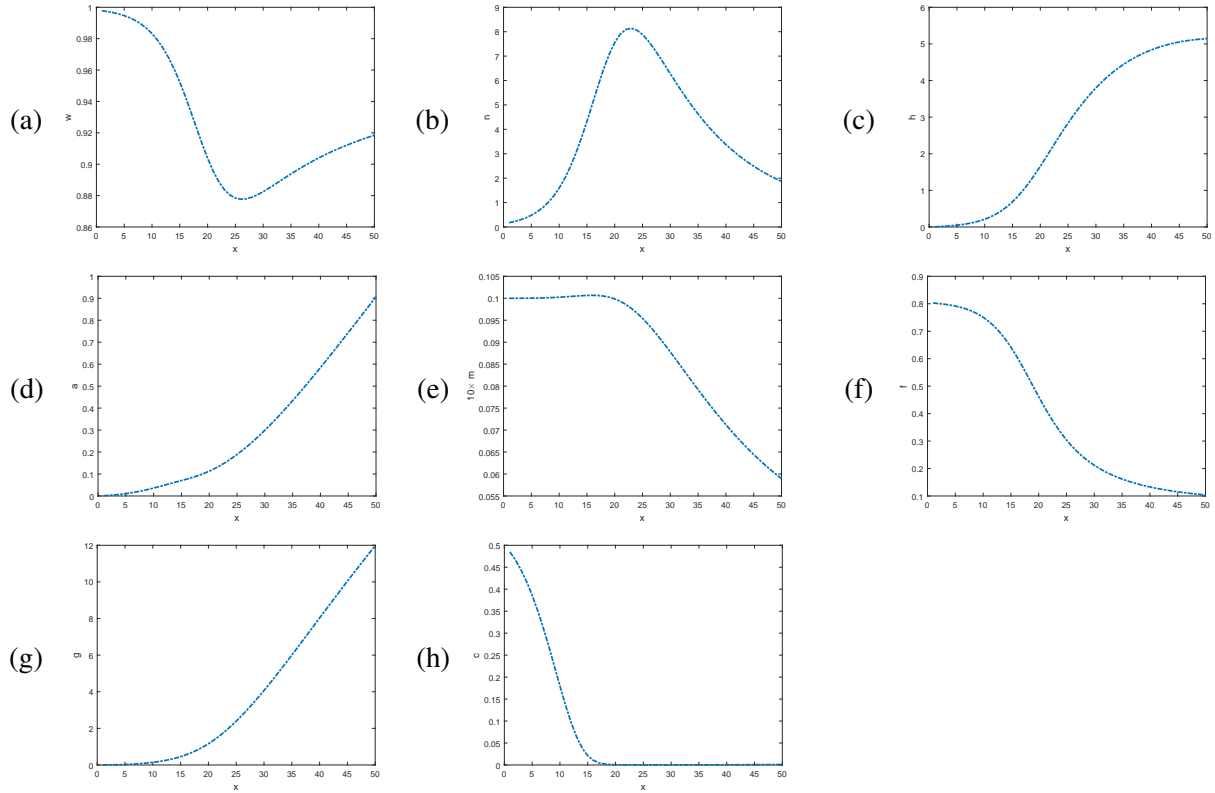
FIGURE 5. Numerical solution of anti-cytotoxic chemotherapy model at $t =$ 5presenting the spatial distributions of: (a) oxygen, (b) normoxic, (c) hypoxic, (d) apoptic, (e) endothelial, (f) extracellular matrix, (g) agiogenic and (h) cytotoxic cells. Parameter values are as given in Table 1.
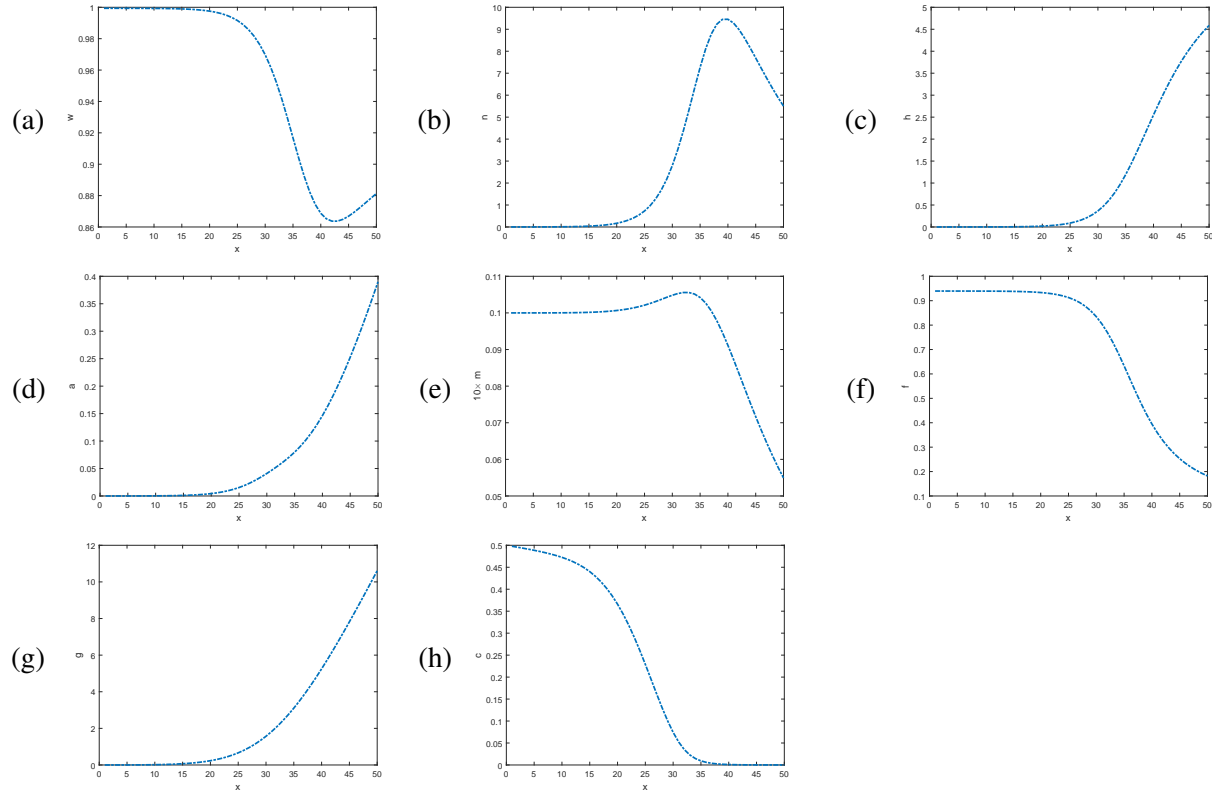
FIGURE 6. Numerical solution of anti-cytotoxic chemotherapy model at $t =$ 10presenting the spatial distributions of: (a) oxygen, (b) normoxic, (c) hypoxic, (d) apoptic, (e) endothelial, (f) extracellular matrix, (g) agiogenic and (h) cytotoxic cells. Parameter values are as given in Table 1.