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A FITTED OPERATOR METHOD FOR TUMOR CELLS DYNAMICS IN THEIR MICRO-ENVIRONMENT

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Abstract. In this paper, we consider a quasi non-linear reaction-diffusion model designed to mimic tumor cells' proliferation and migration under the influence of their micro-environment in vitro. Since the model can be used to generate hypotheses regarding the development of drugs which confine tumor growth, then considering the composition of the model, we modify the model by incorporating realistic effects which we believe can shed more light into the original model. We do this by extending the quasi non-linear reaction-diffusion model to a system of discrete delay quasi non-linear reaction-diffusion model. Thus, we determine the steady states, provide the conditions for global stability of the steady states by using the method of upper and lower solutions and analyze the extended model for the existence of Hopf bifurcation and present the conditions for Hopf bifurcation to occur. Since it is not possible to solve the models analytically, we derive, analyze, implement a fitted operator method and present our results for the extended model. Our numerical method is analyzed for convergence and we find that is of second order accuracy. We present our numerical results for both of the models for comparison purposes.

Keywords: tumor cells; micro-environment; proliferation; migration; upper and low solutions; Hopf bifurcation; fitted operator; stability analysis.

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1. Introduction

The study of cancer disease has led to the development of many cancer models see for instance [14]. Most of the models are developed with one common goals, that is to understand how cancer cells functions. Since a cure to cancerous diseases is still not found, this makes the study of cancer disease an ongoing process. As a result of that, in this paper we are interested in the the study of an interaction of tumor cells, within its own micro-environment. We note that such studies has led to the development of many research work such as optimal control for mathematical models of cancer therapies in [40], computational modeling of interactions between multiple myeloma and the bone micro-environment in [45], the role of the micro-environment in tumor growth and invasion in [24] and current trends in mathematical modeling of tumor-micro-environment interactions: a survey of tools and applications in [34] in the past few recent years. Thus, before highlighting the system of non linear reaction-diffusion models modeling an in-vitro situation of tumor cells and their micro-environment with regard to its growth and metastasis derived and experimented in [23] and simulated in [12], we would like to mention that Friedman and Kim in [12] mentioned that tumor cells proliferate at different rates and migrate in different patterns depending on the micro-environment in which they are embedded. Thus, further work done in the direction of tumor cells embedded in their micro-environments, are for instance the establishment in [6] that as a tumor invades an unsuspecting host, an accumulation of evidence points to an alternative paradigm, where the tumor micro-environment is not an idle bystander, but actively participates in tumor progression and metastasis. In fact, stromal cells and their cytokines coordinate critical pathways that exert important roles in the ability of tumors to invade and metastasize. More information regarding the actively participation of tumor micro-environment in tumor progression and metastasis can also be traced in [4, 26]. Thus understanding the relationship between tumor and its micro-environment may lead to important new therapeutic approaches in controlling the growth and metastasis of cancer. However, tumor micro-environment includes various cell types such as epithelial cells, fibroblasts, myofibroblasts, endothelial cells, and inflammatory cells. These cells communicate with one another and influence each other behavior by means of the cytokines and growth factors they secrete. Thus, in an effort to understand the interaction between tumor cells, fibroblasts and/or myofibroblasts at an early stage of cancer, Friedman and Kim in [12] simulated the model derived in [23] an in-vitro model as

$$
(1)\quad \left.
\begin{aligned}
&\frac{\partial n}{\partial t} = \underbrace{\frac{\partial}{\partial x}\left(D_n \frac{\partial n}{\partial x}\right)}_{\text{Random walk}} - \frac{\partial}{\partial x}\left(\underbrace{\chi_n n \frac{\frac{\partial E}{\partial x}}{\sqrt{1+(\frac{\partial E}{\partial x}/\lambda_E)^2}}}_{\text{Chemotaxis}}\right) \\
&\underbrace{+a_{11}\frac{E^4}{k_E^4+E^4} n(1-n/\kappa)}_{\text{Proliferation}},\ 0<x<L/2, \\
&\frac{\partial f}{\partial t} = \underbrace{\frac{\partial}{\partial x}\left(D_f \frac{\partial f}{\partial x}\right)}_{\text{Random walk}} - \underbrace{a_{21}Gf}_{f\to m} + \underbrace{a_{22}f}_{\text{Proliferation}},\ -L/2<x<0, \\
&\frac{\partial m}{\partial t} = \underbrace{\frac{\partial}{\partial x}\left(D_m \frac{\partial m}{\partial x}\right)}_{\text{Random walk}} - \underbrace{\frac{\partial}{\partial x}\left(\chi_m m \frac{\frac{\partial G}{\partial x}}{\sqrt{1+(\frac{\partial G}{\partial x}/\lambda_G)^2}}\right)}_{\text{Chemotaxis}} + \underbrace{a_{21}Gf}_{f\to m} \\
&+ \underbrace{a_{31}m}_{\text{Proliferation}},\ -L/2<x<0, \\
&\frac{\partial E}{\partial t} = \underbrace{\frac{\partial}{\partial x}\left(D_E \frac{\partial E}{\partial x}\right)}_{\text{Diffusion}} + \underbrace{a_{41}f + Ba_{41}m)}_{\text{Production}} - \underbrace{a_{43}E}_{\text{Decay}},\ -L/2<x<L/2, \\
&\frac{\partial G}{\partial t} = \underbrace{\frac{\partial}{\partial x}\left(D_G \frac{\partial G}{\partial x}\right)}_{\text{Diffusion}} + \underbrace{a_{51}n}_{\text{Production}} - \underbrace{a_{52}G}_{\text{Decay}},\ -L/2<x<L/2,
\end{aligned}
\right\}
$$

where transformed epithelial cells (TECs) and fibroblasts, myfibroblasts are denoted by n and f,m respectively, in equation (1), are placed in a trans-well, separated by a semi-permeable membrane. The membrane has small micro-holes ($\approx 0.4\mu m$ diameter) to allow the epidermal growth factor (EGF) and transformed growth factor (TGF-β)) to pass through the membrane from one compartment to another. These molelcules are denoted by E and G, respectively, and the length of the compartment is denoted by L in equation (1). Friedman and Kim [12] main conclusions' are

(i) fibroblasts enhance proliferation of breast cancer cell lines,

(ii) transformed epithelial cells (TECs) population is sensitive to membrane permeability and to the transformation rate from fibroblasts to myofibroblasts,

(iii) interaction between transformed epithelial cells (TECs) and fibroblasts promotes not only transformed epithelial cells (TECs) proliferation but also the proliferation of fibroblasts and/or myofibroblasts and the transformation from fibroblasts into myofibroblasts.

Eventhough Friedman and Kim [12], did not present their simulation results explicitly, we realised that thier findings are in agreement with assertion in [7, 22], that when epithelial cells are in the breast duct, they are transformed by genetic mutations, from which they begin to form aggregates that secrete higher concentrations of transformed growth factor (TGF-β) and this results into transformation of fibroblasts into myofibroblasts. Consequently, the increased concentration of transformed growth factor (TGF-β) also triggers the fibroblasts and myofibroblasts to secrete higher concentrations of epidermal growth factor (EGF) than in a healthy tissue.

Thus, to capture the higher concentrations of epidermal growth factor (EGF), we believe one has to consider the time required for a complete aggregation of the epithelial cells through the secretion of higher concentrations of epidermal growth factor (EGF) than in a healthy tissue. Denoting the required time by τ, this implies that we extend the quasi non-linear reaction-diffusion model simulated in [12] to mimic tumor cells' proliferation and migration under the influence the micro-environment in vitro in equation (1), to a discrete delay quasi non-linear reaction-diffusion model

$$
(2)\quad \left.\begin{aligned}
&\frac{\partial n}{\partial t}=\frac{\partial}{\partial x}\left(D_n\frac{\partial n}{\partial x}\right)-\frac{\partial}{\partial x}\left(\chi_n n\frac{\frac{\partial E}{\partial x}}{\sqrt{1+(\frac{\partial E}{\partial x}/\lambda_E)^2}}\right)\\
&+a_{11}\frac{E^4}{k_E^4+E^4}n(1-n/\kappa),\ 0<x<L/2,\\
&\frac{\partial f}{\partial t}=\frac{\partial}{\partial x}\left(D_f\frac{\partial f}{\partial x}\right)-a_{21}G(x,t-\tau)f(x,t-\tau)+a_{22}f(x,t-\tau),\ \ -L/2<x<0,\\
&\frac{\partial m}{\partial t}=\frac{\partial}{\partial x}\left(D_m\frac{\partial m}{\partial x}\right)-\frac{\partial}{\partial x}\left(\chi_m m\frac{\frac{\partial G}{\partial x}}{\sqrt{1+(\frac{\partial G}{\partial x}/\lambda_G)^2}}\right)+a_{21}G(x,t-\tau)f(x,t-\tau)\\
&+a_{31}m,\ \ -L/2<x<0,\\
&\frac{\partial E}{\partial t}=\frac{\partial}{\partial x}\left(D_E\frac{\partial E}{\partial x}\right)+a_{41}f(x,t-\tau)+Ba_{41}m(x,t-\tau)-a_{43}E,\ \ -L/2<x<L/2,\\
&\frac{\partial G}{\partial t}=\frac{\partial}{\partial x}\left(D_G\frac{\partial G}{\partial x}\right)+a_{51}n(x,t-\tau)-a_{52}G,\ \ -L/2<x<L/2,
\end{aligned}\right\}
$$

with uniform delay τ. We do not include a delay term τ, in the first equation in equation (2) because we believe the attraction of transformed epithelial cells (TECs) in the direction of the concentration gradient of the epidermal growth factor (EGF) can be observed from the adjusted terms. Thus, the time τ is required for the proliferation of fibroblast into myfibroblasts, which in turn requires some time τ for an increased concentration of transformed growth factor (TGF-β) to triggers the fibroblasts and myofibroblasts to secrete higher concentrations of epidermal growth factor (EGF) should reflects its effects in the growth of the transformed epithelial cells, than in a healthy tissue.

Delay differential equations (DDEs) are widely used for analysis and predictions in various areas of life sciences, see for instance [1], epidemiology see for instance [15], immunology see for instance [35], physiology see for instance [38], and neural networks see for instance [10, 18]. Since time-delays and/or time-lags, can be related to the duration of certain hidden processes like the stages of the life cycle, the time between infection of a cell and the production of new viruses, the duration of the infectious period, the immune period, then introduction of such time-delays in a differential model significantly increases the complexity of the model.

Therefore, our first aim in this paper is to investigate how the uniform time delay τ affects the dynamics of the models in equation (4). By applying the Poincar*é* normal form and the center manifold theorem as in [16] we find conditions on the functions and derive formulas which determine the properties of Hopf bifurcation. More specifically, we show that the semi-positive equilibrium point losses its stability and the system exhibits Hopf bifurcation under certain conditions. Considering the stiffness of system of equations in equation (4), our second aim is therefore, to develop a fitted operator numerical method based on the qualitative features of the models in equation (4), in such a way that the numerical method has wider stability region despite the computational complexities associated with it.

Therefore, the boundary conditions for the original model remain unchanged as provided in [12]. That is the fact that the semi-permeable membrane allows concentrations of epidermal growth factor (EGF) and transformed growth factor (TGF-β) to cross over, is represented by the following boundary conditions at the membrane $x = 0$ as

$$\left.\begin{array}{l} \left(D_n\Delta_n - \chi_n n\frac{\Delta E}{\sqrt{1+(|\Delta E|/\lambda_E)^2}}\right)\cdot\upsilon = 0 \quad \text{at} \quad x = 0+, \\ \\ D_f\Delta f\cdot\upsilon = 0 \quad \left(D_m\Delta_m - \chi_m m\frac{\Delta G}{\sqrt{1+(|\Delta G|/\lambda_G)^2}}\right)\cdot\upsilon = 0 \quad \text{at} \quad x = 0-, \end{array}\right\} \tag{3}$$

and

$$\left.\begin{array}{l} \frac{\partial E^+}{\partial x} = \frac{\partial E^-}{\partial x}, \ -\frac{\partial E^+}{\partial x} + \gamma(E^+ - E^-) = 0, \\ \\ \frac{\partial G^+}{\partial x} = \frac{\partial G^-}{\partial x}, \ -\frac{\partial G^+}{\partial x} + \gamma(g^+ - g^-) = 0, \end{array}\right\} \tag{4}$$

where

$$E(x) = \begin{cases} E^+(x) & \text{if} \quad x > 0, \\ \\ E^-(x) & \text{if} \quad x < 0, \end{cases} \qquad G(x) = \begin{cases} G^+(x) & \text{if} \quad x > 0, \\ \\ G^-(x) & \text{if} \quad x < 0, \end{cases}$$

υ is the outward normal, and γ is a positive parameter which is determined by the size and density of the holes in the membrane. The initial conditions [23] become

$$
\left.
\begin{aligned}
& n(x,0) = 1.0\exp(-40(x-1.0)^2), \text{ on } [0,L/2]\times[-\tau,0], \\
& f(x,0) = 1.0\exp(-40x^2)r_f, \text{ on } [-L/2,0]]\times[-\tau,0], \\
& m(x,0) = 0.00, \text{ on } [-L/2,0]\times[-\tau,0], \\
& E(x,0) = 1.0, \text{ on } [-L/2,L/2]\times[-\tau,0], \\
& G(x,0) = 1.0, \text{ on } [-L/2,L/2]\times[-\tau,0].
\end{aligned}
\right\} \tag{5}
$$

The rest of the paper is organized as follow. Mathematical analysis of the main model is presented in Section 2. A robust numerical scheme based on the 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 model

In this section, we carry out the local stability and Hopf Bifurcation analysis and global stability analysis of the steady states.

Local stability and Hopf Bifurcation analysis

At the steady states the in-vitro trans-well model in equation (2) becomes

$$
\left.\begin{aligned}
& a_{11}\tfrac{E^4}{k_E^4+E^4}n(1-n/\kappa)=0,\ 0<x<L/2,\\
& -a_{21}Gf+a_{22}f=0,\ \ -L/2<x<0,\\
& a_{21}Gf+a_{31}m=0,\ \ -L/2<x<0,\\
& a_{41}f+Ba_{41}m-a_{43}E=0,\ \ -L<x<L,\\
& a_{51}n-a_{52}G=0,\ \ -L<x<L.
\end{aligned}\right\} \tag{6}
$$

which implies that

$$
\left.\begin{aligned}
& n^*=0,\ n^*=\kappa \text{ and } G^*=\tfrac{a_{51}}{a_{52}}\begin{cases}0 \text{ if } n^*=0,\\ \tfrac{a_{51}}{a_{52}}\kappa,\ \text{if } n^*=\kappa,\end{cases} \qquad \text{on } 0<x<L/2,\\
& f^*=m^*=0,\ \text{on } -L/2<x<0, E^*=0,\ \text{on } -L/2<x<L/2.
\end{aligned}\right\} \tag{7}
$$

Therefore, the transwell model in equation (2) has a trivial equilibrium $(0,0,0,0,0)$ and a semi-positive equilibrium $(\kappa,0,0,0,\frac{a_{51}}{a_{52}}\kappa)$. To analyze the stability of the semi-positive equilibrium $(\kappa,0,0,0,\frac{a_{51}}{a_{52}}\kappa)$, the first step is to linearize the in-vitro trans-well model in equation (2) at the steady states (n^*,f^*,m^*,E^*,G^*) as follow:

$$
\frac{\partial U(t)}{\partial t}=d\Delta U(t)+L(U_t), \tag{8}
$$

where

$$
\begin{aligned}
d\Delta &= \begin{bmatrix} \frac{\partial}{\partial x}\left(D_n\frac{\partial n}{\partial x}\right)-\frac{\partial}{\partial x}\left(\chi_n n\frac{\frac{\partial E}{\partial x}}{\sqrt{1+(\frac{\partial E}{\partial x}/\lambda_E)^2}}\right), \frac{\partial}{\partial x}\left(D_f\frac{\partial f}{\partial x}\right),\\ \frac{\partial}{\partial x}\left(D_m\frac{\partial m}{\partial x}\right)-\frac{\partial}{\partial x}\left(\chi_m m\frac{\frac{\partial G}{\partial x}}{\sqrt{1+(\frac{\partial G}{\partial x}/\lambda_G)^2}}\right), \frac{\partial}{\partial x}\left(D_E\frac{\partial E}{\partial x}\right), \frac{\partial}{\partial x}\left(D_G\frac{\partial G}{\partial x}\right)\end{bmatrix},\\
\mathrm{dom}(d\Delta) &= \left\{(n,f,m,E,G)^T:(n,f,m,E,G)\in C([-L/2,L/2]),\mathbb{R}\right\},
\end{aligned}
$$

such that the given boundary conditions are satisfied in $[-L/2, L/2]$ and $L : C([-\tau, 0], X) \to X$ is defined as

$$L(\phi) = \begin{pmatrix} 0\phi_1(0) \\ a_{22}\phi_2(0) - a_{21}G^*\phi_2(-\tau) - a_{21}f^*\phi_5(-\tau) \\ a_{31}\phi_3(0) + a_{21}G^*\phi_2(-\tau) + a_{21}f^*\phi_5(-\tau) \\ -a_{43}\phi_3(0) + a_{41}\phi_2(-\tau) + Ba_{41}\phi_3(-\tau) \\ -a_{52}\phi_5(0) + a_{51}\phi_5(-\tau) \end{pmatrix}, \tag{9}$$

for $\phi = (\phi_1, \phi_2, \phi_3, \phi_4, \phi_5)^T \in C([-\tau, 0], X)$. The characteristic equation of equation in (8) is

$$\lambda y - d\Delta - L(\exp(\lambda y) = 0, \text{ where } y \in \text{ dom}(d\Delta), y \neq 0. \tag{10}$$

Since the boundary conditions in equation (3-4) are of Nuemann type, then the operator $-\Delta$ has eigenvalues $0 = \mu_1 \leq \mu_2 \leq \mu_3 \leq \mu_4 \dots \mu_i \leq \mu_{i+1} \leq \dots$ and $\lim_{i\to\infty} \mu_i = \infty$, with the corresponding eigenfunctions $\Phi(x)$. Substituting

$$y = \sum_{i=0}^{\infty} \Phi(x) \begin{pmatrix} y_{1i} \\ y_{2i} \\ y_{3i} \\ y_{4i} \\ y_{5i} \end{pmatrix} \tag{11}$$

into equation (10) we obtain

$$\begin{pmatrix} 0\phi_1(0) - D_n\mu_i \\ a_{22} - D_f\mu_i - a_{21}G^* \exp(-\lambda\tau) - a_{21}f^* \exp(-\lambda\tau) \\ a_{31} - D_m\mu_i + a_{21}G^* \exp(-\lambda\tau) + a_{21}f^* \exp(-\lambda\tau) \\ -a_{43} - D_E\mu_i + a_{41} \exp(-\lambda\tau) + Ba_{41} \exp(-\lambda\tau) \\ -a_{52} - D_G\mu_i + a_{51} \exp(-\lambda\tau) \end{pmatrix} \begin{pmatrix} y_{1i} \\ y_{2i} \\ y_{3i} \\ y_{4i} \\ y_{5i} \end{pmatrix} = \lambda \begin{pmatrix} y_{1i} \\ y_{2i} \\ y_{3i} \\ y_{4i} \\ y_{5i} \end{pmatrix}. \tag{12}$$

The stability of the positive equilibrium can be determined by the distribution of the roots of (13). It is locally asymptotically stable if all the roots of equation (12) have negative real parts for all $i = 0, 1, 2, 3, \dots$. Obviously, zero is not a root of (12) for all $i = 0, 1, 2, 3, \dots$. When $\tau = 0$, we obtain the eigenvalues as

$$\lambda = -D_n\mu_i,\ -D_f\mu_i - a_{21}G^* + a_{22},\ -D_m\mu_i + a_{31},\ -D_e\mu_i,\ -D_g\mu_i. \tag{13}$$

The eigenvalues in equation (13) are unconditionally asymptotic stable for the steady state $(0,0,0,0,0)$ and conditionally asymptotic stable for the steady state $(\kappa,0,0,0,\frac{a_{51}}{a_{52}}\kappa)$ when $a_{22} < \frac{a_{21}a_{51}}{a_{52}}\kappa$. Thus, the following results.

Theorem 2.1.

(i) The trivial $(0,0,0,0,0)$ steady state is unconditional asymptotic stable.

(ii) If $a_{22} < \frac{a_{21}a_{51}}{a_{52}}\kappa$ holds, the interior equilibrium $(\kappa,0,0,0,\frac{a_{51}}{a_{52}}\kappa)$ of the transwell model in equation (2) is asymptotically stable.

When $\tau \neq 0$, we assume that $\lambda = i\omega, (\omega > 0)$. In view of equation (13), we have

$$i\omega + D_f\mu_k + a_{21}G^*(\cos(\omega\tau) + i\sin(\omega\tau)) - a_{22} = 0, \tag{14}$$

Separating the real and imaginary parts in equation (14), we have

$$i\omega + ia_{21}G^*\sin(\omega\tau) = 0,\ D_f\mu_k + a_{21}G^*\cos(\omega\tau) - a_{22} = 0, \tag{15}$$

which implies that

$$\tau_i = \frac{1}{\omega}\cos^{-1}\left(\frac{a_{22} - D_f\mu_k}{a_{21}G^*} + 2i\pi\right),\ \forall i = 0,1,2,3,\ldots, \tag{16}$$

and we can show that

$$\text{Sign}\left[\text{Re}\left(\frac{\partial\lambda}{\partial\tau}\right)\right] = \text{Sign}\left[\text{Re}\left(\frac{\partial\lambda}{\partial\tau}\right)^{-1}\right]. \tag{17}$$

Squaring on both sides of equation (15), we have

$$\omega^2 + 2\omega a_{21}G^*\sin(\omega\tau) + (a_{21}G^*)^2\sin^2(\omega\tau) = 0,$$

$$(D_f\mu_k - a_{22})^2 + 2(D_f\mu_k - a_{22})(a_{21}G^*\cos(\omega\tau)) + (a_{21}G^*)^2\cos^2(\omega\tau) = 0, \tag{18}$$

Adding the two equations in (18) and simplify we obtain

$$\omega = \sqrt{3(D_f\mu_k - a_{22})^2 + (a_{21}G^*)}. \tag{19}$$

Let $\tau_0 = \min\{\tau_i\}$, the we are able to state the following results.

Lemma 2.1.

(i) If $a_{22} < \frac{a_{21}a_{51}}{a_{52}}\kappa$ hold for $i = 0,1,2,\dots,$ then the equilibrium $(\kappa,0,0,0,\frac{a_{51}}{a_{52}}\kappa)$ of the transwell model in equation (2) is asymptotically stable for all $\tau \geq 0$.

(ii) If $0 \leq \tau_0$, then the equilibrium $(\kappa,0,0,0,\frac{a_{51}}{a_{52}}\kappa)$ of the transwell model in equation (2) is asymptotically stable.

(iii) If $\tau > \tau_0$, then the equilibrium $(\kappa,0,0,0,\frac{a_{51}}{a_{52}}\kappa)$ of the transwell model in equation (2) is unstable.

(iv) The transwell model in equation (2) undergoes a Hopf bifurcation at the equilibrium $(\kappa,0,0,0,\frac{a_{51}}{a_{52}}\kappa)$ for $\tau = \tau_i$, where $i = 0,1,2,\dots$.

Global stability analysis

In this section we mainly prove that the equilibrium $(\kappa,0,0,0,\frac{a_{51}}{a_{52}}\kappa)$ is globally asymptotically stable with the upper and lower solution method in [30, 31]. Let $\vartheta_E = \frac{E^4}{k_E^4+E^4}$, then denoting the reaction functions in equation (2) by $h_j(n,f,m,E,G)$ for $j = 1,2,3,4,5$, then from equation (6) we have

$$\left.\begin{aligned}
&h_1 = a_{11}\vartheta_E n(1-n/\kappa) = 0,\ 0 < x < L/2,\\
&h_2 = -a_{21}Gf + a_{22}f = 0,\ \ -L/2 < x < 0,\\
&h_3 = a_{21}Gf + a_{31}m = 0,\ \ -L/2 < x < 0,\\
&h_4 = a_{41}f + Ba_{41}m - a_{43}E = 0,\ \ -L/2 < x < L/2,\\
&h_5 = a_{51}n - a_{52}G = 0,\ \ -L/2 < x < L/2,
\end{aligned}\right\} \tag{20}$$

and let $S \subset \mathbb{R}_+^5$ such that $S = \{\mathbf{u} \in \mathbb{R}_+^5 : \underline{\mathbf{u}} \leq 0 \leq \bar{\mathbf{u}}\}$ and K_j be any positive constant satisfying

$$K \geq \max\{K_j\} \geq \max\left\{\frac{-\partial h_j}{\partial u_j} : \mathbf{u} = (n,f,m,E,G) \in S\right\},\ j = 1,2,3,4,5.$$

then we have the following results.

Lemma 2.2. Let

$$
\left.\begin{aligned}
&\frac{\partial n}{\partial t}-\frac{\partial}{\partial x}\left(D_n\frac{\partial n}{\partial x}\right)+\frac{\partial}{\partial x}\left(\chi_n n\frac{\frac{\partial E}{\partial x}}{\sqrt{1+(\frac{\partial E}{\partial x}/\lambda_E)^2}}\right)\leq K_1,\ 0<x<L/2,\\
&\frac{\partial f}{\partial t}-\frac{\partial}{\partial x}\left(D_f\frac{\partial f}{\partial x}\right)\leq K_2,\ \ -L/2<x<0,\\
&\frac{\partial m}{\partial t}-\frac{\partial}{\partial x}\left(D_m\frac{\partial m}{\partial x}\right)+\frac{\partial}{\partial x}\left(\chi_m m\frac{\frac{\partial G}{\partial x}}{\sqrt{1+(\frac{\partial G}{\partial x}/\lambda_G)^2}}\right)\leq K_3,\ \ -L/2<x<0,\\
&\frac{\partial E}{\partial t}-\frac{\partial}{\partial x}\left(D_E\frac{\partial E}{\partial x}\right)\leq K_4,\ \ -L/2<x<L/2,\\
&\frac{\partial G}{\partial t}-\frac{\partial}{\partial x}\left(D_G\frac{\partial G}{\partial x}\right)\leq K_5,\ \ -L/2<x<L/2,
\end{aligned}\right\} \tag{21}
$$

then

$$
\begin{aligned}
\lim_{t\to\infty} n(x,t) &= K_1,\ \lim_{t\to\infty} f(x,t)=K_2,\ \lim_{t\to\infty} m(x,t)=K_3,\\
\lim_{t\to\infty} E(x,t) &= K_4,\ \lim_{t\to\infty} G(x,t)=K_5.
\end{aligned}
$$

Theorem 2.2. If $a_{22}<\frac{a_{21}a_{51}}{a_{52}}\kappa$ for the transwell model in equation (2) implies that the equilibrium $(\kappa,0,0,0,\frac{a_{51}}{a_{52}}\kappa)$ is globally asymptotically stable.

Proof: From the maximum principle of parabolic equations, it is known that for any initial value $(n_0(t,x),f_0(t,x),m_0(t,x),E_0(t,x),G_0(t,x))>(0,0,0,0,0)$ the corresponding non-negative solution $(n(t,x),f(t,x),m(t,x),E(t,x),G(t,x))$ is strictly positive for $t>0$. Since $a_{22}<\frac{a_{21}a_{51}}{a_{52}}\kappa$, then we choose $\varepsilon_0\in(0,1)$. Then according to Lemma (2.2.) and the comparison principle of parabolic equations, there exists $t_1>0$ such that, for any $t>t_1$,

$$
\left.\begin{aligned}
&n(x,t) \le K_1 + \varepsilon_0 := \bar{n}(x,t),\ 0 < x < L/2,\\
&f(x,t) \le K_2 + \varepsilon := \bar{f}(x,t),\ -L/2 < x < 0,\\
&m(x,t) \le K_3 + \varepsilon := \bar{m}(x,t),\ -L/2 < x < 0,\\
&E(x,t) \le K_4 + \varepsilon := \bar{E}(x,t),\ -L/2 < x < L/2,\\
&G(x,t) \le K_5 + \varepsilon := \bar{G}(x,t),\ -L/2 < x < L/2,
\end{aligned}\right\} \tag{22}
$$

and

$$
\left.\begin{aligned}
&n(x,t) \ge K_1 - \varepsilon_0 := \underline{n}(x,t),\ 0 < x < L/2,\\
&f(x,t) \ge K_2 - \varepsilon := \underline{f}(x,t),\ -L/2 < x < 0,,\\
&m(x,t) \ge K_3 - \varepsilon := \underline{m}(x,t),\ -L/2 < x < 0,\\
&E(x,t) \ge K_4 - \varepsilon := \underline{E}(x,t),\ -L/2 < x < L/2,\\
&G(x,t) \ge K_5 - \varepsilon := \underline{G}(x,t),\ -L/2 < x < L/2.
\end{aligned}\right\} \tag{23}
$$

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

$$
\begin{aligned}
\underline{n}(x,t) &\le n(x,t) \le \bar{n}(x,t),\ 0 < x < L/2,\ \underline{f}(x,t) \le f(x,t) \le \bar{f}(x,t),\ -L/2 < x < 0,\\
\underline{m}(x,t) &\le m(x,t) \le \bar{m}(x,t),\ -L/2 < x < 0,\ \underline{E}(x,t) \le E(x,t) \le \bar{E}(x,t),\ -L/2 < x < L/2,\\
\underline{G}(x,t) &\le G(x,t) \le \bar{G}(x,t),\ -L/2 < x < L/2.
\end{aligned}
$$

Since $h_j(n,f,m,E,G)$ in equation (20) is a C^1 function of n,f,m,E,G, where h_1 is quasi-monotone non-decreasing in f,m,E,G, h_2 is quasi-monotone non-increasing in n,m,E,G, h_3 is quasi-monotone non-increasing in n,f,E,G, h_4 is quasi-monotone non-decreasing in n,f,m,G and h_5 is quasi-monotone non-decreasing in n,f,m,E, then by the method of upper and lower solutions we know that the system in (2) has a unique global non-negative solution n, f, m, E, G, [30]. Thus,

$$\underline{n}, \bar{n}, \underline{f}, \bar{f}, \underline{m}, \bar{m}, \underline{E}, \bar{E}, \underline{G}, \bar{G}, \tag{24}$$

satisfy

$$\left.\begin{array}{l}
\frac{a_{11}}{\kappa}\bar{E}_4\bar{n}(1-\bar{n}) \leq 0 \leq \frac{a_{11}}{\kappa}\underline{E}\underline{n}(1-\underline{n}),\ 0<x<L/2, \\[2ex]
-a_{21}\underline{G}\bar{f}+a_{22}\bar{f} \leq 0 \leq -a_{21}\bar{G}\underline{f}+a_{22}\underline{f},\ -L/2<x<0, \\[2ex]
a_{21}\underline{G}\underline{f}+a_{31}\bar{m} \leq 0 \leq a_{21}\bar{G}\bar{f}+a_{31}\underline{m},\ -L/2<x<0, \\[2ex]
a_{41}\bar{f}+Ba_{41}\bar{m}-a_{43}\bar{E} \leq 0 \leq a_{41}\underline{f}+Ba_{41}\underline{m}-a_{43}\underline{E},\ -L<x<L, \\[2ex]
a_{51}\bar{n}-a_{52}\bar{G} \leq 0 \leq a_{51}\underline{n}-a_{52}\underline{G},\ -L<x<L.
\end{array}\right\} \tag{25}$$

Therefore, $(\bar{n}, \bar{f}, \bar{m}, \bar{E}, \bar{G})$ and $(\underline{n}, \underline{f}, \underline{m}, \underline{E}, \underline{G})$, are a pair of coupled upper and lower solutions of system (2),[50], respectively. Thus, for any $(\underline{n}, \underline{f}, \underline{m}, \underline{E}, \underline{G}) \leq (n_1, f_1, m_1, E_1, G_1)$ and $(n_2, f_2, m_2, E_2, G_2) \leq (\bar{n}, \bar{f}, \bar{m}, \bar{E}, \bar{G})$ we have

$$\left.\begin{array}{l}
\left|\frac{a_{11}E_1^4 n_1}{k_E^4+E_1^4}(1-\frac{n_1}{\kappa})-(\frac{a_{11}E_2^4 n_2}{k_E^4+E_2^4}(1-\frac{n_2}{\kappa}))\right| \leq K(|E_1-E_2|+|n_1-n_2|), 0<x<L/2, \\
|-a_{21}G_1 f_1+a_{22}f_1-(-a_{21}G_2 f_2+a_{22}f_2)| \leq K(|G_1-G_2|+|f_1-f_2|), -L/2<x<0, \\
|a_{21}G_1 f_1+a_{31}m_1-(a_{21}G_2 f_2+a_{31}m_2)| \leq K(G_1-G_2|+|m_1-m_2|)=0, -L/2<x<0, \\
|a_{41}f_1+Ba_{41}m_1-a_{43}E_1-(a_{41}f_2+Ba_{41}m_2-a_{43}E_2)) \leq K(f_1-f_2|+|m_1-m_2|), -L<x<L, \\
|a_{51}n_1-a_{52}G_1-(a_{51}n_2-a_{52}G_2)| \leq K(|n_1-n_2|+|G_2-G_2|), -L<x<L.
\end{array}\right\}$$

Defining two iteration sequences $(\bar{n},\bar{f},\bar{m},\bar{E},\bar{G})$ and $(\underline{n},\underline{f},\underline{m},\underline{E},\underline{G})$ for $i\geq 1$,

$$
\left.\begin{aligned}
&\bar{n}^{(i)}=\bar{n}^{(i-1)}+(\tfrac{a_{11}}{\kappa}\bar{E}^{(i-1)}\bar{n}^{(i-1)}(1-\bar{n}^{(i-1)}))/K,\ 0<x<L/2,\\
&\bar{f}^{(i)}=\bar{f}^{(i-1)}+(-a_{21}\underline{G}^{(i-1)}\bar{f}^{(i-1)}+a_{22}\bar{f}^{(i-1)})/K,\\
&\\
&\bar{m}^{(i)}=\bar{m}^{(i-1)}+(a_{21}\underline{G}^{(i-1)}\underline{f}^{(i-1)}+a_{31}\bar{m}^{(i-1)})/K,\ \ -L/2<x<0,\\
&\bar{E}^{(i)}=\bar{E}^{(i-1)}+(a_{41}\bar{f}^{(i-1)}+Ba_{41}\bar{m}^{(i-1)}-a_{43}\bar{E}^{(i-1)})/K,\ \ -L<x<L,\\
&\bar{G}^{(i)}=\bar{G}^{(i-1)}+(a_{51}\bar{n}^{(i-1)}-a_{52}\bar{G}^{(i-1)})/K,\ \ -L<x<L,\\
&\underline{n}^{(i)}=\underline{n}^{(i-1)}+(\tfrac{a_{11}}{\kappa}\underline{E}^{(i-1)}\underline{n}_1^{(i-1)}(1-\underline{n}_1^{(i-1)}))/K,\ 0<x<L/2,\\
&\underline{f}^{(i)}=\underline{f}^{(i-1)}+(-a_{21}\bar{G}^{(i-1)}\underline{f}^{(i-1)}+a_{22}\underline{f}^{(i-1)})/K,\ \ -L/2<x<0,\\
&\underline{m}^{(i)}=\underline{m}^{(i-1)}+(a_{21}\bar{G}^{(i-1)}\bar{f}^{(i-1)}+a_{31}\underline{m}^{(i-1)})/K,\ \ -L/2<x<0,\\
&\underline{E}^{(i)}=\underline{E}^{(i-1)}+(a_{41}\underline{f}^{(i-1)}+Ba_{41}\underline{m}^{(i-1)}-a_{43}\underline{E}^{(i-1)})/K,\ \ -L<x<L,\\
&\underline{G}^{(i)}=\underline{G}^{(i-1)}+(a_{51}\underline{n}^{(i-1)}-a_{52}\underline{G}^{(i-1)})/K,\ \ -L<x<L,
\end{aligned}\right\}\tag{26}
$$

where $(\bar{n}^{(0)},\bar{f}^{(0)},\bar{m}^{(0)},\bar{E}^{(0)},\bar{G}^{(0)})=(\bar{n},\bar{f},\bar{m},\bar{E},\bar{G})$ and $(\underline{n}^{(0)},\underline{f}^{(0)},\underline{m}^{(0)},\underline{E}^{(0)},\underline{G}^{(0)})=(\underline{n},\underline{f},\underline{m},\underline{E},\underline{G})$. Thus, for $i\geq 1$

$$
\begin{aligned}
&(\underline{n},\underline{f},\underline{m},\underline{E},\underline{G})\leq(\underline{n}^{(i)},\underline{f}^{(i)},\underline{m}^{(i)},\underline{E}^{(i)},\underline{G}^{(i)})\leq(\underline{n}^{(i+1)},\underline{f}^{(i+1)},\underline{m}^{(i+1)},\underline{E}^{(i+1)},\underline{G}^{(i+1)})\\
&\leq(\bar{n}^{(i+1)},\bar{f}^{(i+1)},\bar{m}^{(i+1)},\bar{E}^{(i+1)},\bar{G}^{(i+1)}\leq(\bar{n}^{(i)},\bar{f}^{(i)},\bar{m}^{(i)},\bar{E}^{(i)},\bar{G}^{(i)})\leq(\bar{n},\bar{f},\bar{m},\bar{E},\bar{G}),
\end{aligned}
$$

and there exist $(\tilde{n}^{(0)},\tilde{f}^{(0)},\tilde{m}^{(0)},\tilde{E}^{(0)},\tilde{G}^{(0)})>(0,0,0,0,0)$ and $(\hat{n}^{(0)},\hat{f}^{(0)},\hat{m}^{(0)},\hat{E}^{(0)},\hat{G}^{(0)})>(0,0,0,0,0)$ such that

$$
\lim_{i\to\infty}\bar{n}=\tilde{n},\ \lim_{i\to\infty}\bar{f}=\tilde{f},\ \lim_{i\to\infty}\bar{m}=\tilde{m},\ \lim_{i\to\infty}\bar{E}=\tilde{E},\ \lim_{i\to\infty}\bar{G}=\tilde{G},
$$

and

$$
\lim_{i\to\infty}\underline{n}=\hat{n},\ \lim_{i\to\infty}\underline{f}=\hat{f},\ \lim_{i\to\infty}\underline{m}=\hat{m},\ \lim_{i\to\infty}\underline{E}=\hat{E},\ \lim_{i\to\infty}\underline{G}=\hat{G},
$$

and

$$\left.\begin{array}{l}\frac{a_{11}}{\kappa}\tilde{E}\tilde{n}(1-\tilde{n})=0,\ \frac{a_{11}}{\kappa}\hat{E}\hat{n}(1-\hat{n})=0,\ 0<x<L/2,\\ -a_{21}\hat{E}\tilde{f}+a_{22}\tilde{f}=0,\ -a_{21}\tilde{G}\hat{f}+a_{22}\hat{f}=0,\ -L/2<x<0,\\ a_{21}\hat{G}\hat{f}+a_{31}\tilde{m}=0,\ a_{21}\tilde{G}\tilde{f}+a_{31}\hat{m}=0,\ -L/2<x<0,\\ a_{41}\tilde{f}+Ba_{41}\tilde{m}-a_{43}\tilde{E}=0,\ a_{41}\hat{f}+Ba_{41}\hat{m}-a_{43}\hat{E}=0,\ -L<x<L,\\ a_{51}\tilde{n}-a_{52}\tilde{G}=0\ a_{51}\hat{n}-a_{52}\hat{G}=0,\ -L<x<L.\end{array}\right\} \tag{27}$$

Since, $(\kappa,0,0,0,\frac{a_{51}}{a_{52}}\kappa)$ is the unique positive constant equilibrium of system (2), it must hold for

$$(\tilde{n},\tilde{f},\tilde{m},\tilde{E},\tilde{G})=(\hat{n},\hat{f},\hat{m},\hat{E},\hat{G})=(\kappa,0,0,0,\frac{a_{51}}{a_{52}}\kappa). \tag{28}$$

Thus, by [30, 31], the solution $(n(x,t),f(x,t),m(x,t),E(x,t),G(x,t))$ of system (2) satisfies

$$\begin{aligned}\lim_{t\to\infty}n(x,t) &= n^*,\ \lim_{t\to\infty}f(x,t)=f^*,\ \lim_{t\to\infty}m(x,t)=m^*,\ \lim_{t\to\infty}E(x,t)=E^*,\\ \lim_{t\to\infty}G(x,t) &= G^*.\end{aligned} \tag{29}$$

Hence, the constant equilibrium $(\kappa,0,0,0,\frac{a_{51}}{a_{52}}\kappa)$ is globally asymptotically stable.

3. Derivation and analysis of the numerical method

In this section, we describe the derivation of the fitted operator method for solving the system in equation (2). We determine an approximation to the derivatives of the functions $n(t,x),f(x,t),m(x,t),E(x,t),G(x,t)$, with respect to the spatial variable x.

Let S_x be a positive integer. Discretize the interval $[-L/2,L/2]$ through the points

$$-L/2=x_0<x_1<x_2<\cdots<x_{s-1}<x_s<x_{s+1}\cdots<x_{S_x-2}<x_{S_x-1}<x_{S_x}=L/2,$$

where the step-size $\Delta x=x_{j+1}-x_j=(L/2+L/2)/S_x$, $j=0,1,\ldots,x_{S_x}$. Let

$$\mathscr{N}_j(t),\mathscr{F}_j(t),\mathscr{M}_j(t),\mathscr{E}_j(t),\mathscr{G}_j(t), \tag{30}$$

denote the numerical approximations of $n(t,x), f(x,t), m(x,t), E(x,t), G(x,t)$. Then we approximate the spatial derivative in the system in (2) by

$$
\left.
\begin{aligned}
&\frac{\partial}{\partial x}\left(D_n\frac{\partial n}{\partial x}-\chi_n n\frac{\frac{\partial E}{\partial x}}{\sqrt{1+(\frac{\partial E}{\partial x}/\lambda_E)^2}}\right)(t,x_j)\approx D_n\frac{\mathscr{N}_{j+1}-2\mathscr{N}_j+\mathscr{N}_{j-1}}{\phi_n^2}\\
&\qquad -\chi_n(D_x^-\mathscr{N}_j)\frac{(D_x^-\mathscr{E}_j)}{\sqrt{1+\left(\frac{D_x^-\mathscr{E}_j}{\lambda_E}\right)^2}}\\
&\qquad -\chi_n\mathscr{N}_j\frac{D_x^+(D_x^-\mathscr{E}_j)}{\left(1+\left(\frac{D_x^-\mathscr{E}_j}{\lambda_E}\right)^2\right)^{3/2}},\\
&\frac{\partial}{\partial x}\left(D_f\frac{\partial f}{\partial x}\right)(t,x_j)\approx D_f\frac{\mathscr{F}_{j+1}-2\mathscr{F}_j+\mathscr{F}_{j-1}}{\phi_f^2},\\
&\frac{\partial}{\partial x}\left(D_m\frac{\partial m}{\partial x}-\chi_m m\frac{\frac{\partial G}{\partial x}}{\sqrt{1+(\frac{\partial G}{\partial x}/\lambda_G)^2}}\right)\approx D_m\frac{\mathscr{M}_{j+1}-2\mathscr{M}_j+\mathscr{M}_{j-1}}{\phi_m^2}\\
&\qquad -\chi_m(D_x^-\mathscr{M}_j)\frac{(D_x^-\mathscr{G}_j)}{\sqrt{1+\left(\frac{D_x^-\mathscr{G}_j}{\lambda_G}\right)^2}}\\
&\qquad -\chi_m\mathscr{M}_j\frac{D_x^+(D_x^-\mathscr{G}_j)}{\left(1+\left(\frac{D_x^-\mathscr{G}_j}{\lambda_G}\right)^2\right)^{3/2}},\\
&\frac{\partial}{\partial x}\left(D_E\frac{\partial E}{\partial x}\right)(t,x_j)\approx D_E\frac{\mathscr{E}_{j+1}-2\mathscr{E}_j+\mathscr{E}_{j-1}}{\phi_E^2},\\
&\frac{\partial}{\partial x}\left(D_G\frac{\partial G}{\partial x}\right)(t,x_j)\approx D_G\frac{\mathscr{G}_{j+1}-2\mathscr{G}_j+\mathscr{G}_{j-1}}{\phi_G^2},
\end{aligned}
\right\}
\tag{31}
$$

where

$$D^+(\cdot)_j=\frac{(\cdot)_{j+1}-(\cdot)_j}{\Delta x},\ D^-(\cdot)_j=\frac{(\cdot)_j-(\cdot)_{j-1}}{\Delta x},$$

and the denominator functions

$$
\begin{aligned}
\phi_n^2 &:= \frac{D_n\Delta x}{\chi_n}\left[\exp(\frac{\chi_n\Delta x}{D_n})-1\right],\ \phi_f^2:=\frac{4}{\rho_f^2}\sin\left(\frac{\rho_f\Delta x}{2}\right)^2,\ \rho_f:=\sqrt{\frac{a_{22}}{D_f}},\\
\phi_m^2 &:= \frac{D_m\Delta x}{\chi_m}\left[\exp(\frac{\chi_m\Delta x}{D_m})-1\right],\ \phi_E^2:=\frac{4}{\rho_e^2}\sinh\left(\frac{\rho_e\Delta x}{2}\right)^2,\ \rho_e:=\sqrt{\frac{a_{43}}{D_e}},\\
\phi_G^2 &:= \frac{4}{\rho_g^2}\sinh\left(\frac{\rho_g\Delta x}{2}\right)^2,\ \rho_g:=\sqrt{\frac{a_{52}}{Dg}}.
\end{aligned}
$$

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

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

where

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

We approximate the time derivative at t_i by

$$\left.\begin{aligned}
&\tfrac{\partial n}{\partial t}(x,t_i) \approx \tfrac{\mathscr{N}_{j+1}^{i+1} - \mathscr{N}_j^i}{\Delta t},\ \tfrac{\partial f}{\partial t}(x,t_i) \approx \tfrac{\mathscr{F}_{j+1}^{i+1} - \mathscr{F}_j^i}{\psi_f},\ \tfrac{\partial m}{\partial t}(x,t_i) \approx \tfrac{\mathscr{M}_{j+1}^{i+1} - \mathscr{M}_j^i}{\psi_m},\\
&\tfrac{\partial E}{\partial t}(x,t_i) \approx \tfrac{\mathscr{E}_{j+1}^{i+1} - \mathscr{E}_j^i}{\psi_E},\ \tfrac{\partial G}{\partial t}(x,t_i) \approx \tfrac{\mathscr{G}_{j+1}^{i+1} - \mathscr{G}_j^i}{\psi_G},
\end{aligned}\right\} \tag{32}$$

where

$$\psi_f = (1 - \exp(-a_{22}\Delta t))/a_{22},\ \psi_E = (1 - \exp(-a_{43}\Delta t))/a_{43},$$

$$\psi_G = (1 - \exp(-a_{52}\Delta t))/a_{52}, \psi_m = (1 - \exp(-a_{31}\Delta t))/a_{31},$$

where we see that $\psi_f \to \Delta t, \psi_E \to \Delta t, \psi_G \to \Delta t,\ \psi_m \to \Delta t$ as $\Delta t \to 0$. The denominator functions in equations (31) and (32) 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., [28, 32, 33] and references therein.

Combining the equation (31) for the spatial derivatives with equation (32) for time derivatives, we obtain

$$
(33)\quad \left.\begin{aligned}
&\frac{\mathcal{N}_j^{i+1}-\mathcal{N}_j^i}{\Delta t} - D_n\frac{\mathcal{N}_{j+1}^{i+1}-2\mathcal{N}_j^{i+1}+\mathcal{N}_{j-1}^{i+1}}{\phi_n^2} = -\chi_n(D_x^+ n_j^i)\frac{(D_x^-\mathcal{E}_j^i)}{\sqrt{1+\left(\frac{D_x^-\mathcal{E}_j^i}{\lambda_E}\right)^2}}\\
&\qquad -\chi_n\mathcal{N}_j^i\frac{D_x^+(D_x^-\mathcal{E}_j^i)}{\left(1+\left(\frac{D_x^-\mathcal{E}_j^i}{\lambda_E}\right)^2\right)^{3/2}}\\
&\qquad +\frac{a_{11}(\mathcal{E}^4)_j^i\mathcal{N}_j^i}{k_E^4+(\mathcal{E}^4)_j^i}(1-\frac{\mathcal{N}_j^i}{\kappa}),\ x\in[x_s,L/2],\\
&\frac{\mathcal{F}_j^{i+1}-\mathcal{F}_j^i}{\psi_f} - D_f\frac{\mathcal{F}_{j+1}^{i+1}-2\mathcal{F}_j^{i+1}+\mathcal{F}_{j-1}^{i+1}}{\phi_f^2} = -a_{21}(\mathcal{H}_G)_j^i(\mathcal{H}_f)_j^i\\
&\qquad +a_{22}(\mathcal{H}_f)_j^i,\ x\in[-\tfrac{L}{2},x_s],\\
&\frac{\mathcal{M}_j^{i+1}-\mathcal{M}_j^i}{\psi_m} - D_m\frac{\mathcal{M}_{j+1}^{i+1}-2\mathcal{M}_j^{i+1}+\mathcal{M}_{j-1}^{i+1}}{\phi_m^2} = -\chi_m(D_x^+\mathcal{M}_j^i)\frac{(D_x^-\mathcal{G}_j^i)}{\sqrt{1+\left(\frac{D_x^-\mathcal{G}_j^i}{\lambda_G}\right)^2}}\\
&\qquad -\chi_m\mathcal{M}_j^i\frac{D_x^+(D_x^-\mathcal{G}_j^i)}{\left(1+\left(\frac{D_x^-\mathcal{G}_j^i}{\lambda_G}\right)^2\right)^{3/2}}\\
&\qquad +a_{21}(\mathcal{H}_G)_j^i(\mathcal{H}_f)_j^i+a_{31}\mathcal{M}_j^i,\ x\in[-\tfrac{L}{2},x_s],\\
&\frac{\mathcal{E}_j^{i+1}-\mathcal{E}_j^i}{\psi_E} - D_E\frac{\mathcal{E}_{j+1}^{i+1}-2\mathcal{E}_j^{i+1}+\mathcal{E}_{j-1}^{i+1}}{\phi_E^2} = a_{41}(\mathcal{H}_f)_j^i+Ba_{41}(\mathcal{H}_m)_j^i-a_{43}\mathcal{E}_j^i,\ x\in[-\tfrac{L}{2},\tfrac{L}{2}],\\
&\frac{\mathcal{G}_j^{i+1}-\mathcal{G}_j^i}{\psi_G} - D_G\frac{\mathcal{G}_{j+1}^{i+1}-2\mathcal{G}_j^{i+1}+\mathcal{G}_{j-1}^{i+1}}{\phi_G^2} = a_{51}(\mathcal{H}_n)_j^i-a_{52}\mathcal{G}_j^i, x\in[-\tfrac{L}{2},\tfrac{L}{2}],\\
&\mathcal{F}^i_{\frac{-L}{2}+1}=\mathcal{F}^i_{\frac{-L}{2}-1},\ \mathcal{G}^i_{\frac{L}{2}+1}=\mathcal{G}^i_{\frac{L}{2}-1}+2\gamma\Delta x\left((\mathcal{G}^+)_{\frac{L}{2}}-(\mathcal{G}^-)_{\frac{L}{2}}\right),\\
&\mathcal{G}^i_{\frac{-L}{2}-1}=(\mathcal{G}^-)^i_{\frac{-L}{2}+1}(1+2\Delta x\gamma),\\
&\mathcal{M}^i_{\frac{-L}{2}+1}=\mathcal{M}^i_{\frac{-L}{2}-1}+2\Delta x\chi_m\mathcal{M}^i_{\frac{-L}{2}}\left(\frac{\mathcal{G}^i_{\frac{-L}{2}+1}-\mathcal{G}^i_{\frac{-L}{2}-1}}{2\Delta x\sqrt{1+\left(\frac{\mathcal{G}^i_{\frac{-L}{2}+1}-\mathcal{G}^i_{\frac{-L}{2}-1}}{2\Delta x\lambda_G}\right)^2}}\right),\\
&\mathcal{E}^i_{\frac{-L}{2}-1}=(\mathcal{E}^-)^i_{\frac{-L}{2}+1}(1+2\Delta x\gamma),\ \mathcal{E}^i_{\frac{L}{2}+1}=\mathcal{E}^i_{\frac{L}{2}-1}+2\gamma\Delta x\left((\mathcal{E}^+)_{\frac{L}{2}}-(\mathcal{E}^-)_{\frac{L}{2}}\right),\\
&\mathcal{N}^i_{\frac{L}{2}+1}=\mathcal{N}^i_{\frac{L}{2}-1}+2\Delta x\chi_n\mathcal{N}^i_{\frac{L}{2}}\left(\frac{\mathcal{E}^i_{\frac{L}{2}+1}-\mathcal{E}^i_{\frac{L}{2}-1}}{2\Delta x\sqrt{1+\left(\frac{\mathcal{E}^i_{\frac{L}{2}+1}-\mathcal{E}^i_{\frac{L}{2}-1}}{2\Delta x\lambda_E}\right)^2}}\right),\ \mathcal{F}^i_{x_s+1}=\mathcal{F}^i_{x_s-1},\\
&\mathcal{M}^i_{x_s+1}=\mathcal{M}^i_{x_s-1}-2\Delta x\chi_m\mathcal{M}^i_{x_s}\left(\frac{\mathcal{G}^i_{x_s+1}-\mathcal{G}^i_{x_s-1}}{2\Delta x\sqrt{1+\left(\frac{\mathcal{G}^i_{x_s+1}-\mathcal{G}^i_{x_s-1}}{2\Delta x\lambda_G}\right)^2}}\right),\\
&\mathcal{N}^i_{x_s-1}=\mathcal{N}^i_{x_s+1}-2\Delta x\chi_n\mathcal{N}^i_{x_s}\left(\frac{\mathcal{E}^i_{x_s+1}-\mathcal{E}^i_{x_s-1}}{2\Delta x\sqrt{1+\left(\frac{\mathcal{E}^i_{x_s+1}-\mathcal{E}^i_{x_s-1}}{2\Delta x\lambda_E}\right)^2}}\right),\\
&\mathcal{N}^0_{x_j}=\exp(-40(x_j-1)^2),\ \mathcal{F}^0_{x_j}=\exp(-40x_j^2)r_f,\ \mathcal{M}^0_{x_j}=0.00,\ \mathcal{E}^0_{x_j}=\mathcal{G}^0_{x_j}=1.00,
\end{aligned}\right\}
$$

where,the no-flux boundary conditions are discretised by means of the central finite difference [5], $j=-L/2,2,\ldots,L/2-1$, $i=0,1,\ldots,T-1$ and

$$(\mathscr{H}_n)^i_j \approx N(t_i-\tau,x_j),\ (\mathscr{H}_f)^i_j \approx F(t_i-\tau,x_j),\ (\mathscr{H}_G)^i_j \approx G(t_i-\tau,x_j),$$
$$(\mathscr{H}_m)^i_j \approx M(t_i-\tau,x_j), \tag{34}$$

are denoting the history functions corresponding to n,f,m,G. The system in equation (33) can further be simplified as

$$\left.\begin{aligned}
&-\tfrac{D_n}{\phi_n^2}\mathscr{N}^{i+1}_{j-1}+\left(\tfrac{1}{\Delta t}+\tfrac{2D_n}{\phi_n^2}\right)\mathscr{N}^{i+1}_{j}-\tfrac{D_n}{\phi_n^2}\mathscr{N}^{i+1}_{j+1}\\
&\qquad=-\chi_n(D_x^- n^i_j)\frac{(D_x^-\mathscr{E}^i_j)}{\sqrt{1+\left(\frac{D_x^-\mathscr{E}^i_j}{\lambda_E}\right)^2}}-\chi_n\mathscr{N}^i_j\frac{D_x^+(D_x^-\mathscr{E}^i_j)}{\left(1+\left(\frac{D_x^-\mathscr{E}^i_j}{\lambda_E}\right)^2\right)^{3/2}}\\
&\qquad+a_{11}\frac{(\mathscr{E}^4)^i_j}{k_E^4+(\mathscr{E}^4)^i_j}\mathscr{N}^i_j(1-\mathscr{N}^i_j/\kappa)+\frac{\mathscr{N}^i_j}{\Delta t},\\
&-\tfrac{D_f}{\phi_f^2}\mathscr{F}^{i+1}_{j-1}+\left(\tfrac{1}{\psi_f}+\tfrac{2D_f}{\phi_f^2}\right)\mathscr{F}^{i+1}_{j}-\tfrac{D_f}{\phi_f^2}\mathscr{F}^{i+1}_{j+1}\\
&\qquad=-a_{21}(\mathscr{H}_G)^i_j(\mathscr{H}_f)^i_j+a_{22}(\mathscr{H}_f)^i_j+\frac{\mathscr{F}^i_j}{\psi_f},\\
&-\tfrac{D_m}{\phi_m^2}\mathscr{M}^{i+1}_{j-1}+\left(\tfrac{1}{\psi_m}+\tfrac{2D_m}{\phi_m^2}\right)\mathscr{M}^{i+1}_{j}-\tfrac{D_m}{\phi_m^2}\mathscr{M}^{i+1}_{j+1}\\
&\qquad=-\chi_m(D_x^-\mathscr{M}^i_j)\frac{(D_x^-\mathscr{G}^i_j)}{\sqrt{1+\left(\frac{D_x^-\mathscr{G}^i_j}{\lambda_G}\right)^2}}-\chi_m\mathscr{M}^i_j\frac{D_x^+(D_x^-\mathscr{G}^i_j)}{\left(1+\left(\frac{D_x^-\mathscr{G}^i_j}{\lambda_G}\right)^2\right)^{3/2}}\\
&\qquad+a_{21}(\mathscr{H}_G)^i_j(\mathscr{H}_f)^i_j+a_{31}\mathscr{M}^i_j+\frac{\mathscr{M}^i_j}{\Delta t},\\
&-\tfrac{D_E}{\phi_E^2}\mathscr{E}^{i+1}_{j-1}+\left(\tfrac{1}{\psi_E}+\tfrac{2D_E}{\phi_E^2}\right)\mathscr{E}^{i+1}_{j}-\tfrac{D_E}{\phi_E^2}\mathscr{E}^{i+1}_{j+1}\\
&\qquad=a_{41}(\mathscr{H}_f)^i_j+Ba_{41}(\mathscr{H}_m)^i_j-a_{43}\mathscr{E}^i_j+\frac{\mathscr{E}^i_j}{\psi_E},\\
&-\tfrac{D_G}{\phi_G^2}\mathscr{G}^{i+1}_{j-1}+\left(\tfrac{1}{\psi_G}+\tfrac{2D_G}{\phi_G^2}\right)\mathscr{G}^{i+1}_{j}-\tfrac{D_G}{\phi_G^2}\mathscr{G}^{i+1}_{j+1}\\
&\qquad=a_{51}(\mathscr{H}_n)^i_j-a_{52}\mathscr{G}^i_j+\frac{\mathscr{G}^i_j}{\psi_G},
\end{aligned}\right\} \tag{35}$$

which can be written as a tridiagonal system given by

$$
\left.
\begin{aligned}
A_n\mathscr{N}_j^{i+1} &= -\chi_n(D_x^- n_j^i)\frac{(D_x^-\mathscr{E}_j^i)}{\sqrt{1+\left(\frac{D_x^-\mathscr{E}_j^i}{\lambda_E}\right)^2}} - \chi_n\mathscr{N}_j^i\frac{D_x^+(D_x^-\mathscr{E}_j^i)}{\left(1+\left(\frac{D_x^-\mathscr{E}_j^i}{\lambda_E}\right)^2\right)^{3/2}} \\
&\quad + a_{11}\frac{(\mathscr{E}^4)_j^i}{k_E^4+(\mathscr{E}^4)_j^i}\mathscr{N}_j^i(1-\mathscr{N}_j^i/\kappa) + \frac{\mathscr{N}_j^i}{\Delta t}, \\
A_f\mathscr{F}_j^{i+1} &= -a_{21}(\mathscr{H}_G)_j^i(\mathscr{H}_f)_j^i + a_{22}(\mathscr{H}_f)_j^i + \frac{\mathscr{F}_j^i}{\psi_f}, \\
A_m\mathscr{M}_j^{i+1} &= -\chi_m(D_x^-\mathscr{M}_j^i)\frac{(D_x^-\mathscr{G}_j^i)}{\sqrt{1+\left(\frac{D_x^-\mathscr{G}_j^i}{\lambda_G}\right)^2}} - \chi_m\mathscr{M}_j^i\frac{D_x^+(D_x^-\mathscr{G}_j^i)}{\left(1+\left(\frac{D_x^-\mathscr{G}_j^i}{\lambda_G}\right)^2\right)^{3/2}} \\
&\quad + a_{21}(\mathscr{H}_G)_j^i(\mathscr{H}_f)_j^i + a_{31}\mathscr{M}_j^i + \frac{\mathscr{M}_j^i}{\Delta t}, \\
A_E\mathscr{E}_j^{i+1} &= a_{41}(\mathscr{H}_f)_j^i + Ba_{41}(\mathscr{H}_m)_j^i - a_{43}\mathscr{E}_j^i + \frac{\mathscr{E}_j^i}{\psi_E}, \\
A_G\mathscr{G}_j^{i+1} &= a_{51}(\mathscr{H}_n)_j^i - a_{52}\mathscr{G}_j^i + \frac{\mathscr{G}_j^i}{\psi_G},
\end{aligned}
\right\} \tag{36}
$$

where

$$
\left.
\begin{aligned}
A_n &= \text{Tri}\left(-\frac{D_n}{\phi_n^2}, \frac{1}{\Delta t} + \frac{2D_n}{\phi_n^2}, -\frac{D_n}{\phi_n^2}\right),\ A_f = \text{Tri}\left(-\frac{D_f}{\phi_f^2}, \frac{1}{\psi_f} + \frac{2D_f}{\phi_f^2}, -\frac{D_f}{\phi_f^2}\right), \\
A_m &= \text{Tri}\left(-\frac{D_m}{\phi_m^2}, \frac{1}{\psi_m} + \frac{2D_m}{\phi_m^2}, -\frac{D_m}{\phi_m^2}\right),\ A_E = \text{Tri}\left(-\frac{D_E}{\phi_E^2}, \frac{1}{\psi_E} + \frac{2D_E}{\phi_E^2}, -\frac{D_E}{\phi_E^2}\right), \\
A_G &= \text{Tri}\left(-\frac{D_G}{\phi_G^2}, \frac{1}{\psi_G} + \frac{2D_G}{\phi_G^2}, -\frac{D_G}{\phi_G^2}\right).
\end{aligned}
\right\} \tag{37}
$$

On the interval $[0,\tau]$ the delayed arguments $t_n-\tau$ belong to $[-\tau,0]$, and therefore the delayed variables in equation (34) are evaluated directly from the history functions

$$n^0(t,x), f^0(t,x), m^0(t,x), G^0(t,x),$$

as

$$
\begin{aligned}
(\mathscr{H}_n)_j^i &\approx n^0(t_i-\tau,x_j),\ (\mathscr{H}_f)_j^i \approx f^0(t_i-\tau,x_j),\ (\mathscr{H}_m)_j^i \approx m^0(t_i-\tau,x_j), \\
(\mathscr{H}_G)_j^i &\approx G^0(t_i-\tau,x_j), \qquad (38)
\end{aligned}
$$

and equation (36) becomes

$$
(39)\qquad \left.\begin{aligned}
A_n\mathscr{N}_j^{i+1} &= -\chi_n(D_x^- n_j^i)\frac{(D_x^-\mathscr{E}_j^i)}{\sqrt{1+\left(\frac{D_x^-\mathscr{E}_j^i}{\lambda_E}\right)^2}} - \chi_n\mathscr{N}_j^i\frac{D_x^+(D_x^-\mathscr{E}_j^i)}{\left(1+\left(\frac{D_x^-\mathscr{E}_j^i}{\lambda_E}\right)^2\right)^{3/2}}\\
&\quad +a_{11}\frac{(\mathscr{E}^4)_j^i}{k_E^4+(\mathscr{E}^4)_j^i}\mathscr{N}_j^i(1-\mathscr{N}_j^i/\kappa)+\frac{\mathscr{N}_j^i}{\Delta t},\\
A_f\mathscr{F}_j^{i+1} &= -a_{21}G^0(t_i-\tau,x)f^0(t_i-\tau,x)+a_{22}f^0(t_i-\tau,x)+\frac{\mathscr{F}_j^i}{\psi_f},\\
A_m\mathscr{M}_j^{i+1} &= -\chi_m(D_x^-\mathscr{M}_j^i)\frac{(D_x^-\mathscr{G}_j^i)}{\sqrt{1+\left(\frac{D_x^-\mathscr{G}_j^i}{\lambda_G}\right)^2}} - \chi_m\mathscr{M}_j^i\frac{D_x^+(D_x^-\mathscr{G}_j^i)}{\left(1+\left(\frac{D_x^-\mathscr{G}_j^i}{\lambda_G}\right)^2\right)^{3/2}}\\
&\quad +a_{21}G^0(t_i-\tau,x)f^0(t_i-\tau,x)+a_{31}\mathscr{M}_j^i+\frac{\mathscr{M}_j^i}{\Delta t},\\
A_E\mathscr{E}_j^{i+1} &= a_{41}f^0(t_i-\tau,x)+Ba_{41}m^0(t_i-\tau,x)-a_{43}\mathscr{E}_j^i+\frac{\mathscr{E}_j^i}{\psi_E},\\
A_G\mathscr{G}_j^{i+1} &= a_{51}n^0(t_i-\tau,x)-a_{52}\mathscr{G}_j^i+\frac{\mathscr{G}_j^i}{\psi_G}.
\end{aligned}\right\}
$$

Let s be the largest integer such that $\tau_s \leq \tau$. By using the system equation (39) we can compute $\mathscr{N}_j^i, \mathscr{F}_j^i, \mathscr{M}_j^i, \mathscr{E}_j^i, \mathscr{G}_j^i$ for $1 \leq i \leq s$. Up to this stage, we interpolate the data

$$
\begin{aligned}
&(t_0,\mathscr{N}_j^0),\,(t_1,\mathscr{N}_j^1),\ldots,(t_s,\mathscr{N}_j^s),\,(t_0,\mathscr{F}_j^0),\,(t_1,\mathscr{F}_j^1),\ldots,(t_s,\mathscr{F}_j^s),\\
&(t_0,\mathscr{M}_j^0),\,(t_1,\mathscr{M}_j^1),\ldots,(t_s,\mathscr{M}_j^s),\,(t_0,\mathscr{E}_j^0),\,(t_1,\mathscr{E}_j^1),\ldots,(t_s,\mathscr{E}_j^s),\,(t_0,\mathscr{G}_j^0),\,(t_1,\mathscr{G}_j^1),\ldots,(t_s,\mathscr{G}_j^s),
\end{aligned}
$$

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

$$
\mathscr{N}_j^i=\varphi_n(t_i,x_j),\ \mathscr{F}_j^i=\varphi_f(t_i,x_j),\ \mathscr{M}_j^i=\varphi_m(t_i,x_j),\ \mathscr{E}_j^i=\varphi_E(t_i,x_j)\ \mathscr{G}_j^i=\varphi_G(t_i,x_j),
$$

for all $i = 0,1,\ldots,s$ and $j = -L/2,2,\ldots,L/2-1$.

For $i = s+1, s+2, \ldots, T-1$, when we move from level i to level $i+1$ we extend the definitions of the cubic Hermite spline $\varphi_j(t)$ to the point

$$
(t_i+\Delta t,(\mathscr{H}_n)_j^i,t_i+\Delta t,(\mathscr{H}_f)_j^i,t_i+\Delta t,(\mathscr{H}_m)_j^i,t_i+\Delta t,(\mathscr{H}_G)_j^i).
$$

Then the history terms $(\mathscr{H}_n)^i_j, (\mathscr{H}_f)^i_j, (\mathscr{H}_M)^i_j, (\mathscr{H}_G)^i_j$ can be approximated by the functions $(\varphi_n)_j(t_i-\tau), (\varphi_m)_j(t_i-\tau), (\varphi_m)_j(t_i-\tau), (\varphi_G)_j(t_i-\tau)$ for $i \geq s$. This implies that,

$$
\begin{aligned}
(\mathscr{H}_n)^i_j &\approx (\varphi_n)_j(t_i-\tau),\ (\mathscr{H}_f)^i_j \approx (\varphi_f)_j(t_i-\tau),\ (\mathscr{H}_m)^i_j \approx (\varphi_m)_j(t_i-\tau), \\
(\mathscr{H}_G)^i_j &\approx (\varphi_G)_j(t_i-\tau), \qquad (40)
\end{aligned}
$$

and equation (39) becomes

$$
\left.
\begin{aligned}
A_n\mathscr{N}^{i+1}_j &= -\chi_n(D^-_x n^i_j)\frac{(D^-_x\mathscr{E}^i_j)}{\sqrt{1+\left(\frac{D^-_x\mathscr{E}^i_j}{\lambda_E}\right)^2}} - \chi_n\mathscr{N}^i_j\frac{D^+_x(D^-_x\mathscr{E}^i_j)}{\left(1+\left(\frac{D^-_x\mathscr{E}^i_j}{\lambda_E}\right)^2\right)^{3/2}} \\
&\quad +a_{11}\frac{(\mathscr{E}^4)^i_j}{k^4_E+(\mathscr{E}^4)^i_j}\mathscr{N}^i_j(1-\mathscr{N}^i_j/\kappa)+\frac{\mathscr{N}^i_j}{\Delta t}, \\
A_f\mathscr{F}^{i+1}_j &= -a_{21}(\varphi_G)(t_i-\tau)(\varphi_f)(t_i-\tau)+a_{22}(\varphi_f)(t_i-\tau)+\frac{\mathscr{F}^i_j}{\psi_f}, \\
A_m\mathscr{M}^{i+1}_j &= -\chi_m(D^-_x\mathscr{M}^i_j)\frac{(D^-_x\mathscr{G}^i_j)}{\sqrt{1+\left(\frac{D^-_x\mathscr{G}^i_j}{\lambda_G}\right)^2}} - \chi_m\mathscr{M}^i_j\frac{D^+_x(D^-_x\mathscr{G}^i_j)}{\left(1+\left(\frac{D^-_x\mathscr{G}^i_j}{\lambda_G}\right)^2\right)^{3/2}} \\
&\quad +a_{21}(\varphi_G)(t_i-\tau)(\varphi_f)(t_i-\tau)+a_{31}\mathscr{M}^i_j+\frac{\mathscr{M}^i_j}{\Delta t}, \\
A_E\mathscr{E}^{i+1}_j &= a_{41}(\varphi_f)(t_i-\tau)+Ba_{41}(\varphi_m)(t_i-\tau)-a_{43}\mathscr{E}^i_j+\frac{\mathscr{E}^i_j}{\psi_E}, \\
A_G\mathscr{G}^{i+1}_j &= a_{51}(\varphi_n)(t_i-\tau)-a_{52}\mathscr{G}^i_j+\frac{\mathscr{G}^i_j}{\psi_G},
\end{aligned}
\right\} \qquad (41)
$$

where

$$
\begin{aligned}
\varphi_n(t_i-\tau) &= [(\mathscr{H}_n)^i_1,(\mathscr{H}_n)^i_2\ldots,(\mathscr{H}_n)^i_{\frac{L}{2}-1}]',\ \varphi_f(t_i-\tau)=[(\mathscr{H}_f)^i_{\frac{-L}{2}},(\mathscr{H}_f)^i_{\frac{-L}{2}+1}\ldots,(\mathscr{H}_f)^i_{x_0-1}]', \\
\varphi_m(t_i-\tau) &= [(\mathscr{H}_m)^i_{\frac{-L}{2}},(\mathscr{H}_m)^i_{\frac{-L}{2}+1}\ldots,(\mathscr{H}_m)^i_{x_0-1}]',\ \varphi_E(t_i-\tau)=[\mathscr{E}^i_{\frac{-L}{2}},\mathscr{E}^i_{\frac{-L}{2}+1}\ldots,\mathscr{E}^i_{\frac{L}{2}-1}]', \\
\varphi_G(t_i-\tau) &= [(\mathscr{H}_G)^i_{\frac{-L}{2}},(\mathscr{H}_G)^i_{\frac{-L}{2}+1}\ldots,(\mathscr{H}_G)^i_{\frac{L}{2}-1}]'.
\end{aligned}
$$

Our FOFDM is then consists of equations (36)-(41). Rewriting the FOFDM as a system of equations we have

$$\left.\begin{aligned} A_n\mathscr{N} &= F_n,\\ A_f\mathscr{F} &= F_f,\\ A_m\mathscr{M} &= F_m,\\ A_E\mathscr{E} &= F_E,\\ A_G\mathscr{G} &= F_G, \end{aligned}\right\} \tag{42}$$

where

$$\left.\begin{aligned}
F_n &= -\chi_n(D_x^- n_j^i)\frac{(D_x^-\mathscr{E}_j^i)}{\sqrt{1+\left(\frac{D_x^-\mathscr{E}_j^i}{\lambda_E}\right)^2}} - \chi_n\mathscr{N}_j^i\frac{D_x^+(D_x^-\mathscr{E}_j^i)}{\left(1+\left(\frac{D_x^-\mathscr{E}_j^i}{\lambda_E}\right)^2\right)^{3/2}}\\
&\quad +a_{11}\frac{(\mathscr{E}^4)_j^i}{k_E^4+(\mathscr{E}^4)_j^i}\mathscr{N}_j^i(1-\mathscr{N}_j^i/\kappa)+\frac{\mathscr{N}_j^i}{\Delta t},\\
F_f &= -a_{21}(\varphi_G)(t_i-\tau)(\varphi_f)(t_i-\tau)+a_{22}(\varphi_f)(t_i-\tau)+\frac{\mathscr{F}_j^i}{\psi_f},\\
F_m &= -\chi_m(D_x^-\mathscr{M}_j^i)\frac{(D_x^-\mathscr{G}_j^i)}{\sqrt{1+\left(\frac{D_x^-\mathscr{G}_j^i}{\lambda_G}\right)^2}} - \chi_m\mathscr{M}_j^i\frac{D_x^+(D_x^-\mathscr{G}_j^i)}{\left(1+\left(\frac{D_x^-\mathscr{G}_j^i}{\lambda_G}\right)^2\right)^{3/2}}\\
&\quad +a_{21}(\varphi_G)(t_i-\tau)(\varphi_f)(t_i-\tau)+a_{31}\mathscr{M}_j^i+\frac{\mathscr{M}_j^i}{\Delta t},\\
F_E &= a_{41}(\varphi_f)(t_i-\tau)+Ba_{41}(\varphi_m)(t_i-\tau)-a_{43}\mathscr{E}_j^i+\frac{\mathscr{E}_j^i}{\psi_E},\\
F_G &= a_{51}(\varphi_n)(t_i-\tau)-a_{52}\mathscr{G}_j^i+\frac{\mathscr{G}_j^i}{\psi_G}.
\end{aligned}\right\}$$

We see that the local truncation errors $(\varsigma_n)^i_j, (\varsigma_f)^i_j, (\varsigma_m)^i_j, (\varsigma_E)^i_j, (\varsigma_G)^i_j$ are given by

$$\left.\begin{aligned}
&(\varsigma_n)^i_j = (A_n n)^i_j - (F_n)^i_j = (A_n(n-\mathscr{N}))^i_j,\\
&(\varsigma_f)^i_j = (A_f f)^i_j - (F_f)^i_j = A_f(f-\mathscr{F})^i_j,\\
&(\varsigma_m)^i_j = (A_m m)^i_j - (F_m)^i_j = (A_m(m-\mathscr{M}))^i_j,\\
&(\varsigma_E)^i_j = (A_E E)^i_j - (F_E)^i_j = (A_E(E-\mathscr{E}))^i_j,\\
&(\varsigma_G)^i_j = (A_G G)^i_j - (F_G)^i_j = (A_G(G-\mathscr{G}))^i_j,
\end{aligned}\right\} \tag{43}$$

Therefore,

$$\left.\begin{aligned}
&\max_{i,j}|n^i_j - \mathscr{N}^i_j| \leq ||A_n^{-1}|| \max_{i,j}|(\varsigma_n)^i_j|,\\
&\max_{i,j}|f^i_j - \mathscr{F}^i_j| \leq ||A_f^{-1}|| \max_{i,j}|(\varsigma_f)^i_j|,\\
&\max_{i,j}|m^i_j - \mathscr{M}^i_j| \leq ||A_m^{-1}|| \max_{i,j}|(\varsigma_m)^i_j|,\\
&\max_{i,j}|E^i_j - \mathscr{E}^i_j| \leq ||A_E^{-1}|| \max_{i,j}|(\varsigma_E)^i_j|,\\
&\max_{i,j}|G^i_j - \mathscr{G}^i_j| \leq ||A_G^{-1}|| \max_{i,j}|(\varsigma_G)^i_j|,
\end{aligned}\right\} \tag{44}$$

where

$$
\left.
\begin{aligned}
&\max_{i,j}|(\varsigma_n)^i_j| \leq \tfrac{(\Delta t)}{2}|n_t(\xi)| - D_n\tfrac{(\Delta x)^2}{12}|n_{xxxx}(\zeta)|,\ x\in[x_s, L/2],\\
&\max_{i,j}|(\varsigma_f)^i_j| \leq \tfrac{(\Delta t)}{2}|f_t(\xi)| - D_f\tfrac{(\Delta x)^2}{12}|f_{xxxx}(\zeta)|,\ x\in[-\tfrac{L}{2}, x_s],\\
&\max_{i,j}|(\varsigma_m)^i_j| \leq \tfrac{(\Delta t)}{2}|m_t(\xi)| - D_m\tfrac{(\Delta x)^2}{12}|n_{xxxx}(\zeta)|,\ x\in[-\tfrac{L}{2}, x_s],\\
&\max_{i,j}|(\varsigma_E)^i_j| \leq \tfrac{(\Delta t)}{2}|E_t(\xi)| - D_E\tfrac{(\Delta x)^2}{12}|E_{xxxx}(\zeta)|,\ x\in[-\tfrac{L}{2}, \tfrac{L}{2}],\\
&\max_{i,j}|(\varsigma_G)^i_j| \leq \tfrac{(\Delta t)}{2}|G_t(\xi)| - D_G\tfrac{(\Delta x)^2}{12}|n_{xxxx}(\zeta)|, x\in[-\tfrac{L}{2}, \tfrac{L}{2}],
\end{aligned}
\right\} \tag{45}
$$

for $t_{i-1} \leq \xi \leq t_{i+1}$ and $x_{j-1} \leq \zeta \leq x_{j+1}$. Moreover by [41] we have

$$
||A_n^{-1}|| \leq \Xi_n,\ ||A_f^{-1}|| \leq \Xi_f, ||A_m^{-1}|| \leq \Xi_m,\ ||A_E^{-1}|| \leq \Xi_E,\ ||A_G^{-1}|| \leq \Xi_G. \tag{46}
$$

Using (45) and (46) in (44), we obtain the following results.

Theorem 3.1. Let

$$
F_n(x,t), F_f(x,t), F_m(x,t), F_E(x,t), F_G(x,t),
$$

be sufficiently smooth functions so that $n(x,t), f(x,t), m(x,t), E(x,t), G(x,t) \in C^{1,2}([1,L]\times[1,T])$. Let $(\mathscr{N}^i_j, \mathscr{F}^i_j, \mathscr{M}^i_j, \mathscr{E}^i_j, \mathscr{G}^i_j)$, $j = 1,2,\dots L, i = 1,2,\dots T$ be the approximate solutions to (3), obtained using the FOFDM with $\mathscr{N}^0_j = n^0_j, \mathscr{F}^0_j = f^0_j, \mathscr{M}^0_j = m^0_j, \mathscr{E}^0_j = E^0_j, \mathscr{G}^0_j = G^0_j$. Then there exists $\Xi_n, \Xi_f, \Xi_m, \Xi_E, \Xi_G$ independent of the step sizes Δt and Δx such that

$$
\left.
\begin{aligned}
&\max_{i,j}|n_j^i-\mathscr{N}_j^i| \le \Xi_n[\tfrac{(\Delta t)}{2}|n_t(\xi)|-D_n\tfrac{(\Delta x)^2}{12}|n_{xxxx}(\zeta)|],\\
&\max_{i,j}|f_j^i-\mathscr{F}_j^i| \le \Xi_f[\tfrac{(\Delta t)}{2}|f_t(\xi)|-D_f\tfrac{(\Delta x)^2}{12}|f_{xxxx}(\zeta)|],\\
&\max_{i,j}|m_j^i-\mathscr{M}_j^i| \le \Xi_m[\tfrac{(\Delta t)}{2}|m_t(\xi)|-D_m\tfrac{(\Delta x)^2}{12}|n_{xxxx}(\zeta)|],\\
&\max_{i,j}|E_j^i-\mathscr{E}_j^i| \le \Xi_E[\tfrac{(\Delta t)}{2}|E_t(\xi)|-D_E\tfrac{(\Delta x)^2}{12}|E_{xxxx}(\zeta)|],\\
&\max_{i,j}|G_j^i-\mathscr{G}_j^i| \le \Xi_G[\tfrac{(\Delta t)}{2}|G_t(\xi)|-D_G\tfrac{(\Delta x)^2}{12}|n_{xxxx}(\zeta)|],
\end{aligned}
\right\}
\tag{47}
$$

and this conclude the analysis of our FOFDM.

4. Numerical results and discussions

We set $x_{S_x} = t_{S_t} = 80$ and time $t = 25$ or $t = 30$. Then using the parameter values in Table 1 ([21]) we first take $L = 5 < T = 20$ and we present our numerical results of the model without delay (1) in Figure 1 and Figure 2, respectively.

For $L = T = 5$ and time $t = 25, 30$, we present our numerical results in Figure 3 ($\tau \equiv 0$), Figure 4 and for $L = 20 > T = 5$, our numerical results are presented in Figure 5 ($\tau \equiv 0$) at time $t = 25$.

Similarly, for $L = 5 < T = 20$, time $t = 25$ and $\tau = 5$, we present our numerical results in Figure 6 and for $\tau = 20$ we present our results in Figure 7.

For $L = 5 = T$, time $t = 25$ and $\tau = 5$, we present our numerical results in Figure 8, for $L = 20 = T$ we present our results in Figure 9, for $t = 25$ and $\tau = 15$ and $L = 20 = T$ we present our results in Figure 10.

Finally, we present our numerical results for $L = 20 > T = 5$ at time $t = 25$ for $\tau = 5, 25$ in Figure 11 and Figure 12.

In the figures for the original model in equation (1), that is Figure 1 to Figure 5 we see that the behaviour for the fibroblasts and myfibroblasts are zero almost for entire portion of their compartment, but eventually rise sharply near the end of the compartment in which they are embedded. One notable fact is the fibroblast grows to a very high hieght than the myfibroblasts. However, for the Transformed epithelial cells we see the oscilations type of behaviour near the preamable membrane when the compartment is lesser than or equal to the time taken for the experiment. However, the oscillation decreases to one sharp peak when the length of the compartment is greater than the the time to be taken for this experiment. For the excreted molecules, we also see a bigger peaks as compare to the restricted cells for the case when the length of the compartment is lesser, equal to the time required by this experiment. However, when we increase the length of the compartment to be bigger than the the time required then we see the excreted molecules grow sharply with slight decrease and increase till their turning point toward the end of the compartment.

For the modified model in equation (2), that is from Figure 6 to Figure 12 we see the following notable feautures. That is the osculations behaviour of the Transformed Epithelial cells are prominent for the case of the compartment being lesser than the time required by this experiment as compare to the behaviour of the vice versa of the length of the compartment to time required by this experiment. However, for the fibroblasts and myfibroblast cells their behaviours remains similar to that of the original model in equation (1). For the excreted molecules we see that their concentration are inverted in Figure 6, as compare to their corresponding behaviours in Figure 1. However, when we increase the delay, we see that the concentration of the Epidermal growth factor smoothes out better than its behaviour when there is no delay. Similarly for the concentration of the Transformed growth factor. These behaviours becomes more prominent as we increases the delay around the specified length of the compartment and time.

In these experiments we see that the interaction of the two concentrations enhances the growth of the Epidermal growth factor molecules. However, such an essential growth is more explicit when a delay term is inclusive in the modeling of these nature.

5. Conclusion

In this paper, we consider a less complicated model simulated in [12] with the aim of shedding more light into the interaction between transformed epithelial cells, fibroblasts and myfibroblasts cells at an early stage of cancer disease. We deemed it essential to incorporate some of the crucial transformations ought to take take place during the experiment carried out in [23]. Such incorporation of some crucial transformations, led the original model to be transformed to a system of non-linear delay parabolic partial differential equations. We analysed the resulting system of non-linear delay parabolic partial differential equations and determined the global stability conditions for our resulting system. Consequently, we were able to derive the a fitted operator finite difference method (FOFDM) for solving the modified system in equation (2). Our main findings are more vivid, eventhough they are indeed in agreement with the presented experimental results found in [12] as well as in [7, 22]. More essentially, the indirect role played by the incorporation of a delay term (τ) in the extended model in equation (2) through the behaviours of the molecules are more informative than what is presented in [12]. Thus, in our views, this work should be seen as the first attempt to shed more light into the behavior of the micro-environment of tumor cells, which in turn contributes toward understanding this complicated infection.

Conflict of Interests The authors declare that there is no conflict of interests.

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REFERENCES

[1] H.T. Banks, J.E. Banks, E. John, R. Bommarco, A.N. Laubmeier, N.J. Myers, M. Rundlöf, K. Tillman, Modeling bumble bee population dynamics with delay differential equations, Ecol. Model. 351 (2017), 14-23.

[2] F. Boccardo, G. Petti, A. Lunardi and A. Rubagotti, Enterolactone in breast cyst fluid: correlation with EGF and breast cancer risk, Breast Cancer Res. 79(1) (2003), 17-23.

[3] K. Bottger, H. Hatzikirou, A. Chauviere and A. Deutsch, Investigation of the migration/proliferation dichotomy and its impact on avascular glioma invasion, Math. Model. Nat. Phenom. 7(1) (2012), 105-135.

[4] R.J. Buchsbaum and S.Y. Oh, Breast cancer-associated fibroblasts: Where we are and where we need to go, Cancers, 8 (2016), 19.

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

[6] J. Cheng and L. Weiner, Tumours and their micro-environments: tilling the soil Commentary re: A.M. Scott et al., A Phase I dose-escalation study of sibrotuzumab in patients with advanced or metastatic fibroblast activation protein-positive cancer, Cancer Res. 9(5) (2003), 1590-1595.

[7] B. Dalal, P. Keown and A. Greenberg, Immunocytochemical localization of secreted transforming growth factor-beta 1 to the advancing edges of primary tumours and to lymph node metastases of human mammary carcinoma, Amer. J. Pathology, 143(2) (1993), 381-389.

[8] T. Faria, Normal forms and Hopf bifurcation for partial differential equations with delays, Trans. Amer. Math. Soc. 352(5) (2000), 2217-2238.

[9] T. Faria and L.T. Magalhães, Normal forms for retarded functional-differential equations with parameters and applications to Hopf bifurcation, J. Differ. Equations 122(2) (1995), 181-200.

[10] U. Foryś, N.Z. Bielczyk, K. Piskała, M. Płomecka and J. Poleszczuk, Impact of Time Delay in Perceptual Decision-Making: Neuronal Population Modeling Approach, Complexity 2017 (2017), Article ID 4391587.

[11] A. Friedman, Cancer as multifaceted disease, Math. Model. Nat. Phenom. 7(1) (2012), 3-28.

[12] A. Friedman and Y. Kim, Tumor Cells Proliferation and migration under the influence of their micro-environment, Math. Biosci. Eng. 8(2) (2011), 371-383.

[13] A. Friedman and G. Lolas, Analysis of a Mathematical Model of Tumour Lymphangiogenesis, Math. Models Methods Appl. Sci. 15(1) (2005), 95-107.

[14] K. Goebel and N.D. Merner, A monograph proposing the use of canine mammary tumours as a model for the study of hereditary breast cancer susceptibility genes in humans, Veterinary Med. Sci. 3(2) (2017), 51-62.

[15] S.A. Gourley, Y. Kuang and J.D. Nagy, Dynamics of a delay differential equation model of hepatitis B virus infection, J. Biol. Dyn. 2(2) (2008), 140-153.

[16] B. D. Hassard, N. D. Kazarinoff, and Y. H. Wan, Theory and Applications of Hopf Bifurcation, Cambridge University Press, Cambridge, UK, 1981.

[17] A. Hooff, Stromal involvement in malignant growth, Adv. Cancer Res. 50 (1988), 159-196.

[18] A. Jafarian, M. Mokhtarpour and D. Baleanu, Artificial neural network approach for a class of fractional ordinary differential equation, Neural Comput. Appl. 28(4) (2017), 765-773.

[19] P. Jones, Extracellular matrix and tenascin-C in pathogenesis of breast cancer, Lancet, 357(9273) (2001), 1992-1994.

[20] E. Khain and L.M. Sander, Dynamics and pattern formation in invasive tumor growth, Phys. Rev. Lett. 96 (2006), 188103.

[21] Y. Kim and A. Friedman, Interaction of tumor with its micro-environment: A mathematical model, Bull. Math. Biol. 72 (2010), 1029-1068.

[22] Y. Kim, J. Wallace, F. Li, M. Ostrowski and A. Friedman, Transformed epithelial cells and fibroblasts/myofibroblasts interaction in breast tumor: A mathematical model and experiments, J. Math. Biol. 61 (2009), 401-21.

[23] Y. Kim, J. Wallace, F. Li, M. Ostrowski and A. Friedman, Transformed epithelial cells and fibroblasts/myofibroblasts interaction in breast tumor: A mathematical model and experiments, J. Math. Biol. 61(3) (2010), 401-421.

[24] Y. Kim, M.A. Stolarsk, H.G. Othmer, The role of the micro-environment in tumor growth and invasion, Prog Biophys. Molecular Biol. 106 (2011), 353-379.

[25] H. Lee, A.S. Silva, S.Concilio, Y. Li, M. Slifker, R.A. Gatenby, and J.D. Cheng, Evolution of tumor invasiveness: The Adaptive tumor micro-environment landscape model, Cancer Res. 71 (2011), 6327-6337.

[26] H.J. Lin and J. Lin, Seed-in-soil: Pancreatic cancer influenced by tumor micro-environment, Cancers 9 (2017), 93.

[27] X.D. Lin, J.W. So, and J.H. Wu, Centre manifolds for partial differential equations with delays, Proc. Royal Soc. Edinburgh A: Math. 122(3-4) (1992), 237-254.

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

[29] C.V. Pao, Dynamics of nonlinear parabolic system with time delays, Journal of Mathematical Analysis and Applications 198 (1996) 751-779.

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

[31] C.V. Pao, Convergence of solutions of reaction-diffusion systems with time delays, Nonlinear Analysis 48 (2002), 349-362.

[32] K.C. Patidar, On the use of non-standard finite difference methods, Journal of Difference Equations and Applications 11 (2005) 735-758.

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

[34] K.A. Rejniak and L.J. McCawley, Current trends in mathematical modeling of tumor-micro-environment interactions: a survey of tools and applications, Exp. Biol. Med. 235(4) (2010), 411-423.

[35] F.A. Rihan and and N.F. Rihan, Dynamics of Cancer-Immune System with External Treatment and Optimal Control, J. Cancer Sci. Therapy 8(10) (2016), 257-261.

[36] A. Sadlonova, Z. Novak, M. Johnson, D. Bowe, S. Gault, G. Page, J. Thottassery, D. Welch and A. Frost, Breast fibroblasts modulate epithelial cell proliferation in three-dimensional in vitro co-culture, Breast Cancer Res. 7 (2004), R46-R59.

[37] M. Samoszuk, Z. Tan and G. Chorn, Clonogenic growth of human breast cancer cells co-cultured in direct contact with serum-activated fibroblasts, Breast Cancer Res. 7 (2005), R274-R283.

[38] K. Schmitt, Delay and Functional Differential Equations and Their Applications Academic Press New York and London 1972.

[39] L. Schwarz, J. Wright, M. Gingras, P. Kondaia, D. Danielpour, M. Pimentel, M. Sporn and A. Greenberg, Aberrant TGF-beta production and regulation in metastatic malignancy, Growth Factors 3(2) (1990), 115-127.

[40] H. Schättler and U. Ledzewic, Optimal control for mathematical models of cancer therapies, Springer, USA, 2010.

[41] 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.

[42] A.M. Stein, T. Demuth, D. Mobley, M. Berens and L.M. Sander, A mathematical model of glioblastoma tumor spheroid invasion in a three-dimensional in vitro experiment, Biophys. J. 92 (2007), 356-365.

[43] A.G. Taylor and A.C. Hindmarsh, User Documentation for Kinsol, A Nonlinear Solver for Sequential and Paraller Computers Center for Applied Scientific Computing, USA, 1998.

[44] L. Wakefield, D. Smith, T. Masui, C. Harris and M. Sporn, Distribution and modulation of the cellular receptor for transforming growth factor-beta, J. Cell Biol. 105(2) (1987), 965-975.

[45] Y. Wang, P. Pivonka, P.R. Buenzli, D.W. Smith and C.R. Dunstan, Computational modeling of interactions between multiple myeloma and the bone micro-environment, Plos One 6(11) (2011), e27494.

[46] M.X. Wang, Nonlinear Partial Differential Equations of Parabolic Type, Science Press, Beijing, China 1993.

[47] J. Wu, Theory and Applications of Partial Functional-Differential Equations, Applied Mathematical Sciences, Springer, New York, USA, 1996.

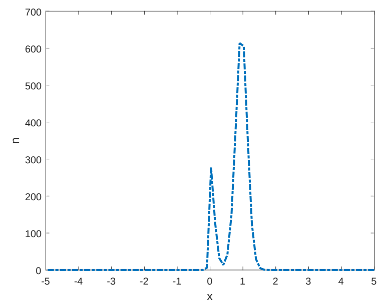
[48] Y. Yang, O. Dukhanina, B. Tang, M. Mamura, J. Letterio, J. MacGregor, S. Patel, S. Khozin, Z. Liu, J. Green, M. Anver, G. Merlino and L. Wakefield, Lifetime exposure to a soluble TGF-β antagonist protects mice against metastasis without adverse side effects, J. Clinical Invest. 109(12) (2002), 1607-1615.

[49] M. Yashiro, K. Ikeda, M. Tendo, T. Ishikawa and K. Hirakawa, Effect of organ-specific fibroblasts on proliferation and differentiation of breast cancer cells, Breast Cancer Res.d Treat. 90 (2005), 307-313.

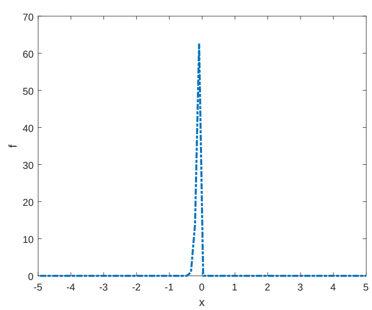
[50] Q.X. Ye and Z.Y. Li, Introduction to Reaction-Diffusion Equations, Science Press, Beijing, China, 1990.

TABLE 1. Parameter values used for the transwell model

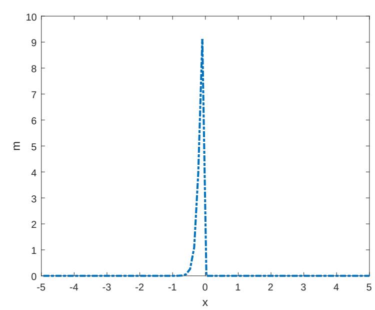
$D_n = 3.6 \times 10^{-4}$	$\chi_n = 3.6 \times 10^{-8}$	$\lambda_E = 1.00$	$a_{11} = 0.69$
$\kappa = 2.88 \times 10^3$	$k_E = 3.32$	$D_f = 6.12 \times 10^{-5}$	$a_{21} = 2.61 \times 10^{-2}$
$a_{22} = 1.58 \times 10^{-2}$	$D_m = 6.12 \times 10^{-4}$	$\chi_m = 3.96 \times 10^{-6}$	$a_{31} = 4.53 \times 10^{-3}$
$\lambda_G = 1.00$	$D_e = 5.98 \times 10^{-1}$	$a_{41} = 1.26$	$a_{43} = 2.89 \times 10^{-2}$
$B = 5.00$	$D_g = 3.6 \times 10^{-1}$	$a_{51} = 2.03 \times 10^{-1}$	$a_{52} = 2.89 \times 10^{-2}$



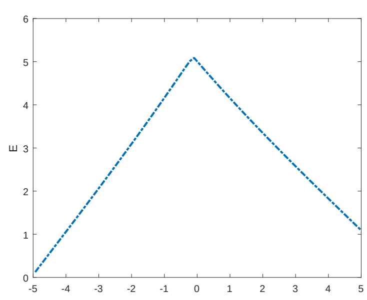
(a) Behaviour of Transformed Epithelial cells (TECs)



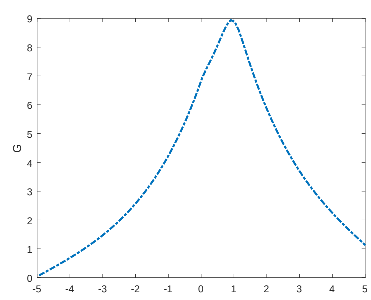
(b) Behaviour of Fibroblasts cells



(c) Behaviour of Myfibroblasts cells

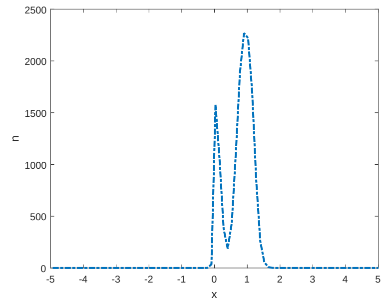


(d) Behaviour of the concentration of Epidermal Growth Factor molecules (EGF)

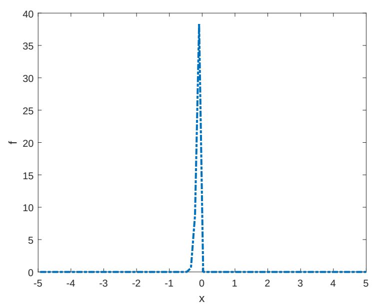


(e) Behaviour of the concentration of Transformed Growth Factor molecules (TGF-β)

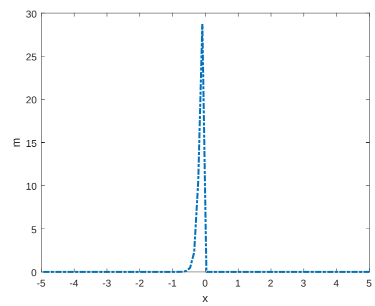
FIGURE 1. Numerical solution of the system in (2) without delay at time (t) = 25 for $L < T$.



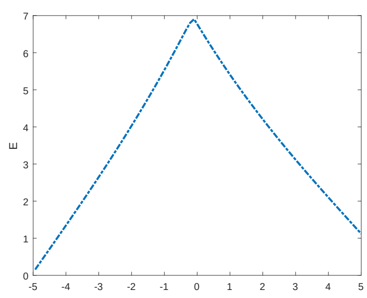
(a) Behaviour of Transformed Epithelial cells (TECs)



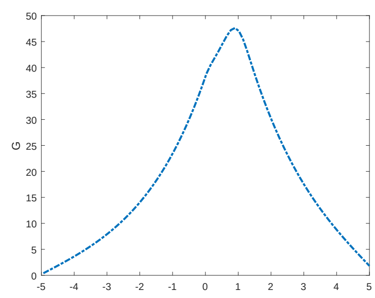
(b) Behaviour of Fibroblasts cells



(c) Behaviour of Myfibroblasts cells

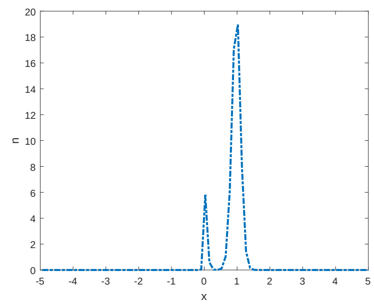


(d) Behaviour of the concentration of Epidermal Growth Factor molecules (EGF)

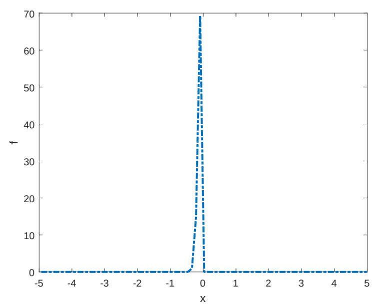


(e) Behaviour of the concentration of Transformed Growth Factor molecules (TGF-β)

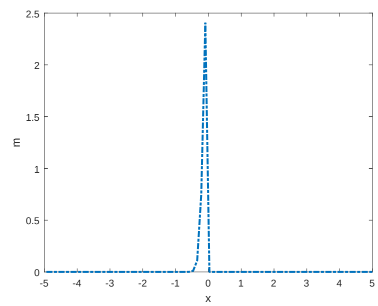
FIGURE 2. Numerical solution of the system in (2) without delay at time (t) = 30 for $L < T$.



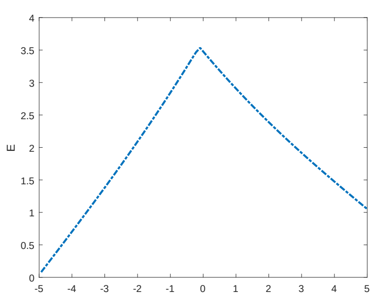
(a) Behaviour of Transformed Epithelial cells (TECs)



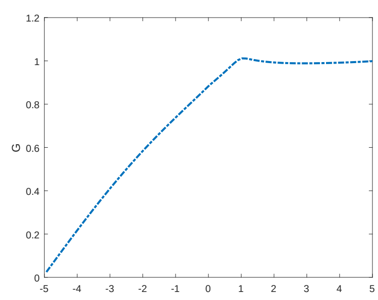
(b) Behaviour of Fibroblasts cells



(c) Behaviour of Myfibroblasts cells

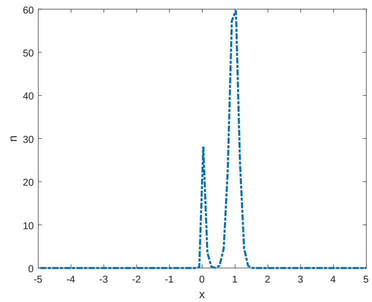


(d) Behaviour of the concentration of Epidermal Growth Factor molecules (EGF)

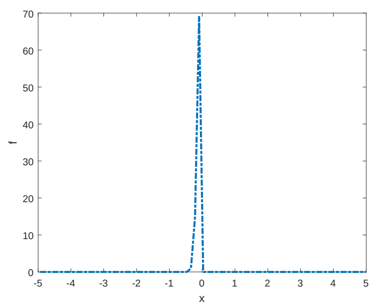


(e) Behaviour of the concentration of Transformed Growth Factor molecules (TGF-β)

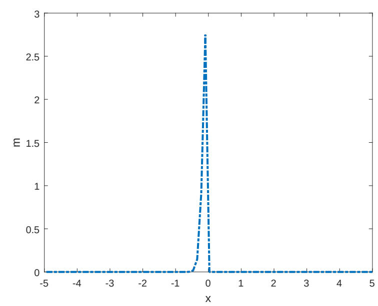
FIGURE 3. Numerical solution of the system in (2) without delay at time (t) = 25 for $L = T$.



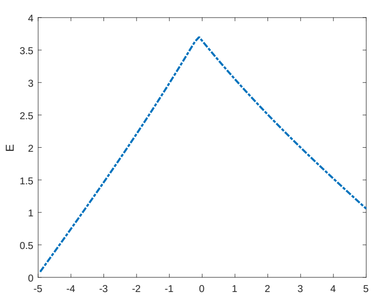
(a) Behaviour of Transformed Epithelial cells (TECs)



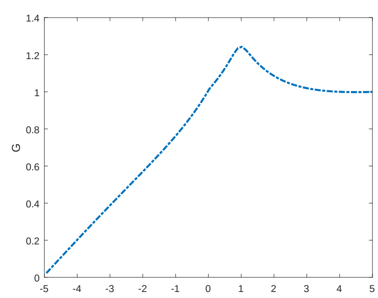
(b) Behaviour of Fibroblasts cells



(c) Behaviour of Myfibroblasts cells

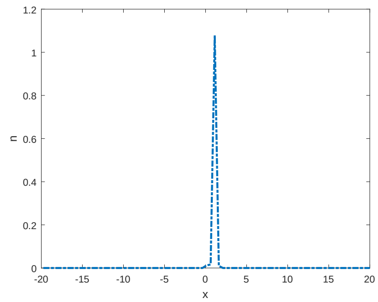


(d) Behaviour of the concentration of Epidermal Growth Factor molecules (EGF)

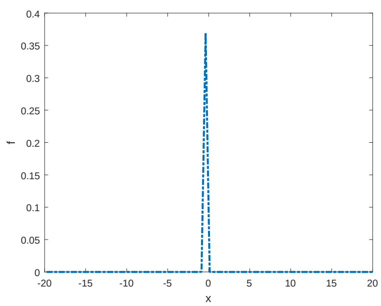


(e) Behaviour of the concentration of Transformed Growth Factor molecules (TGF-β)

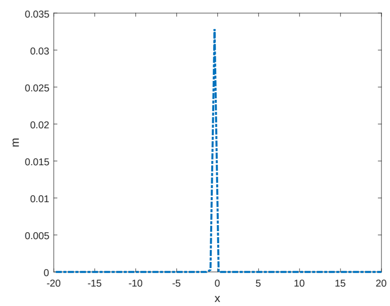
FIGURE 4. Numerical solution of the system in (2) without delay at time (t) = 30 for $L = T$.



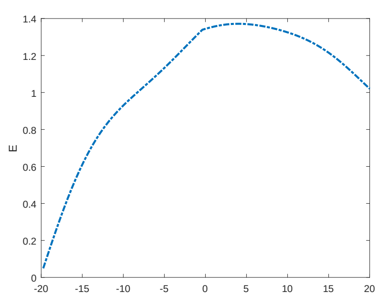
(a) Behaviour of Transformed Epithelial cells (TECs)



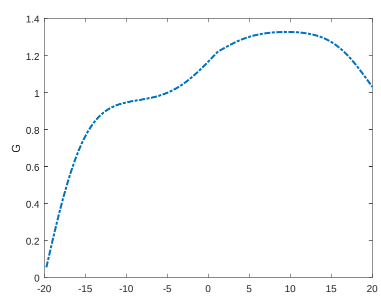
(b) Behaviour of Fibroblasts cells



(c) Behaviour of Myfibroblasts cells

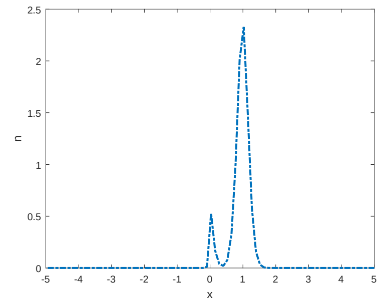


(d) Behaviour of the concentration of Epidermal Growth Factor molecules (EGF)

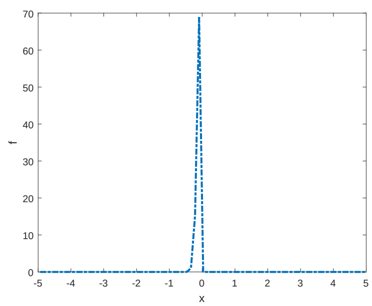


(e) Behaviour of the concentration of Transformed Growth Factor molecules (TGF-β)

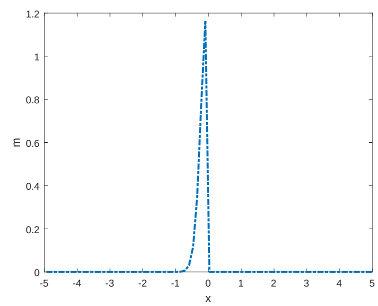
FIGURE 5. Numerical solution of the system in (2) without delay at time (t) = 25 for $L > T$.



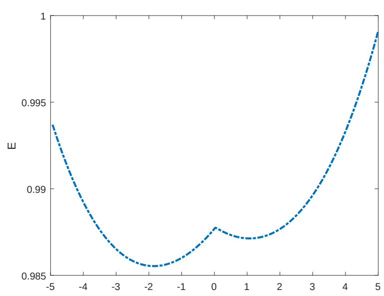
(a) Behaviour of Transformed Epithelial cells (TECs)



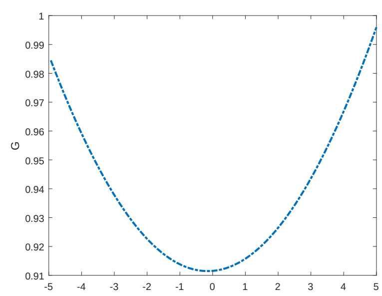
(b) Behaviour of Fibroblasts cells



(c) Behaviour of Myfibroblasts cells

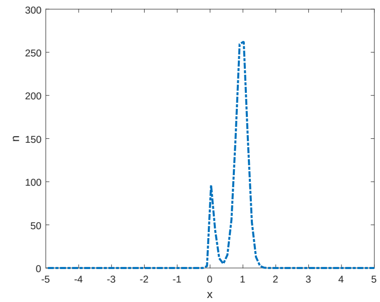


(d) Behaviour of the concentration of Epidermal Growth Factor molecules (EGF)

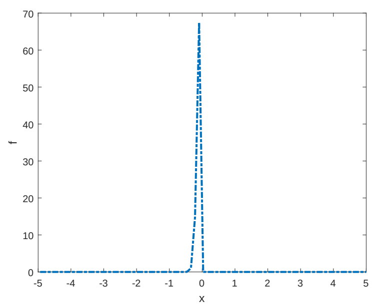


(e) Behaviour of the concentration of Transformed Growth Factor molecules (TGF-β)

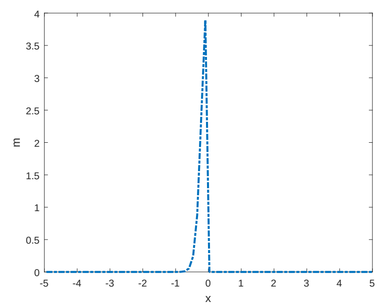
FIGURE 6. Numerical solution of the system in (2) with delay=5 for $L < T$.



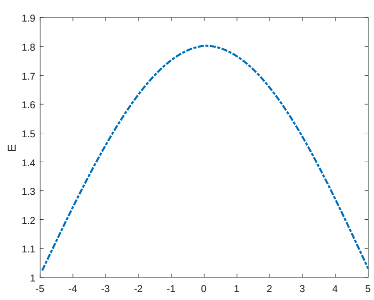
(a) Behaviour of Transformed Epithelial cells (TECs)



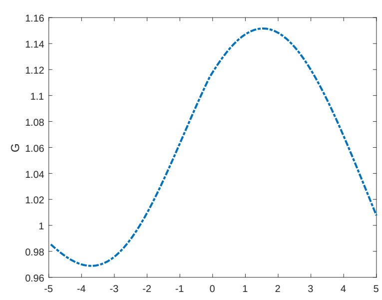
(b) Behaviour of Fibroblasts cells



(c) Behaviour of Myfibroblasts cells

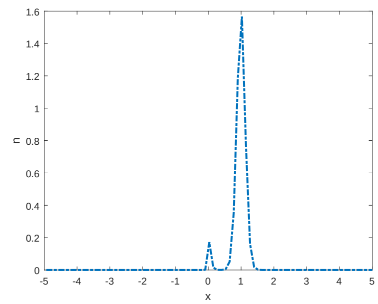


(d) Behaviour of the concentration of Epidermal Growth Factor molecules (EGF)

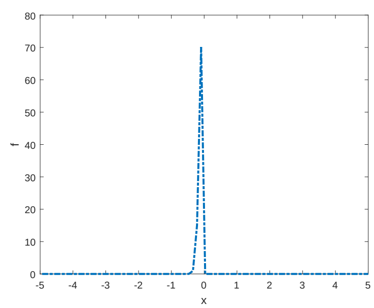


(e) Behaviour of the concentration of Transformed Growth Factor molecules (TGF-β)

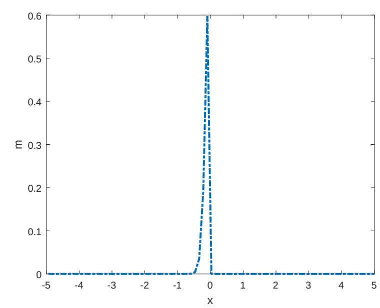
FIGURE 7. Numerical solution of the system in (2) with delay=20 for $L < T$ at $time = 25$.



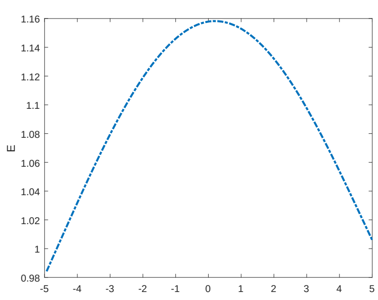
(a) Behaviour of Transformed Epithelial cells (TECs)



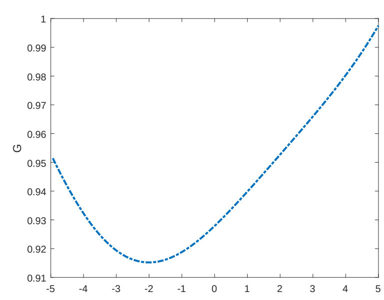
(b) Behaviour of Fibroblasts cells



(c) Behaviour of Myfibroblasts cells

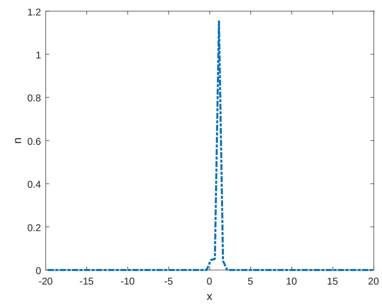


(d) Behaviour of the concentration of Epidermal Growth Factor molecules (EGF)

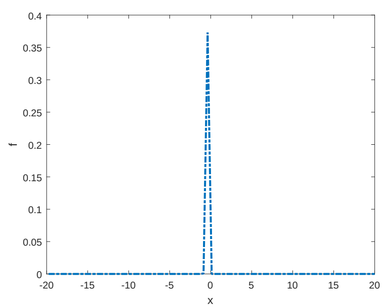


(e) Behaviour of the concentration of Transformed Growth Factor molecules (TGF-β)

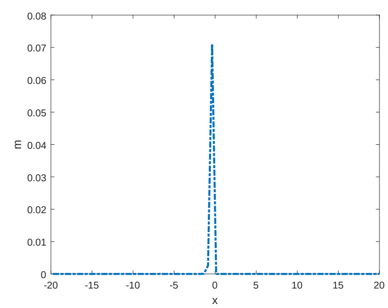
FIGURE 8. Numerical solution of the system in (2) with delay=5 for $L = T$ at $t = 25$.



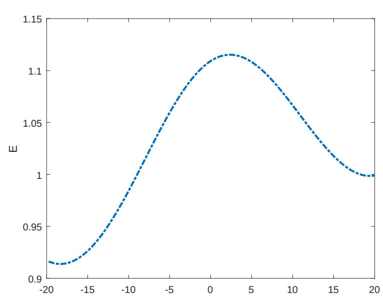
(a) Behaviour of Transformed Epithelial cells (TECs)



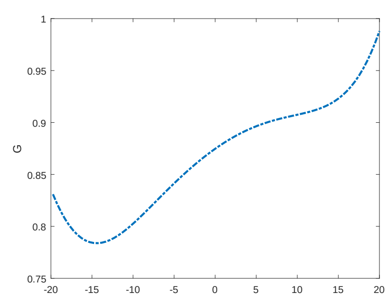
(b) Behaviour of Fibroblasts cells



(c) Behaviour of Myfibroblasts cells

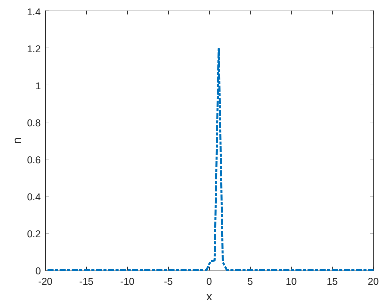


(d) Behaviour of the concentration of Epidermal Growth Factor molecules (EGF)

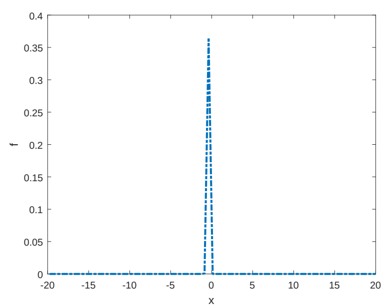


(e) Behaviour of the concentration of Transformed Growth Factor molecules (TGF-β)

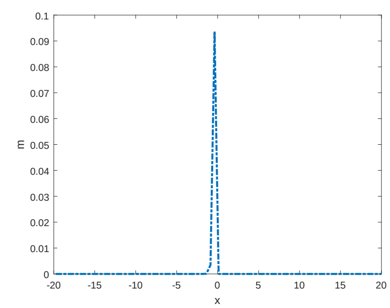
FIGURE 9. Numerical solution of the system in (2) with delay=5 for $L = T$ at $t = 25$.



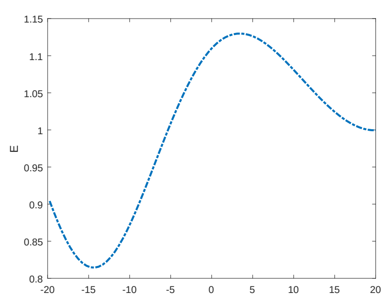
(a) Behaviour of Transformed Epithelial cells (TECs)



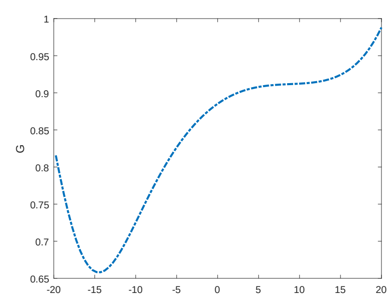
(b) Behaviour of Fibroblasts cells



(c) Behaviour of Myfibroblasts cells

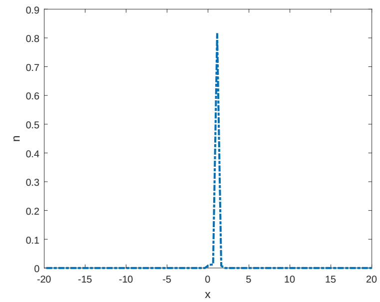


(d) Behaviour of the concentration of Epidermal Growth Factor molecules (EGF)

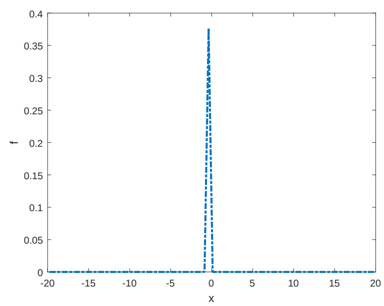


(e) Behaviour of the concentration of Transformed Growth Factor molecules (TGF-β)

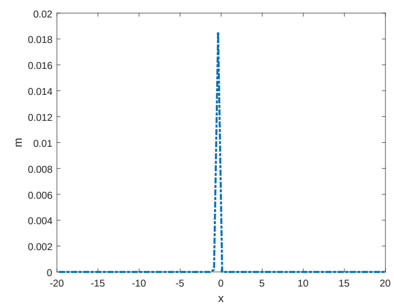
FIGURE 10. Numerical solution of the system in (2) with delay=15 for $L = T$ at $t = 25$.



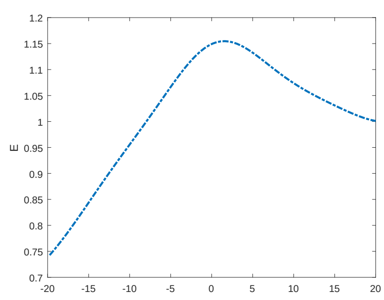
(a) Behaviour of Transformed Epithelial cells (TECs)



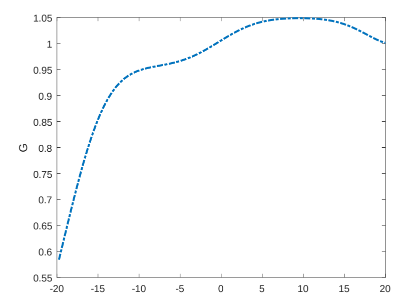
(b) Behaviour of Fibroblasts cells



(c) Behaviour of Myfibroblasts cells

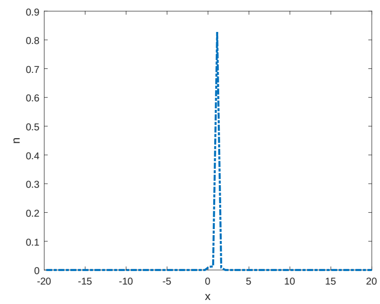


(d) Behaviour of the concentration of Epidermal Growth Factor molecules (EGF)

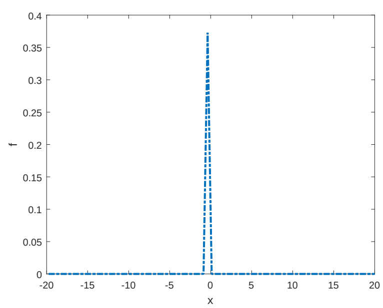


(e) Behaviour of the concentration of Transformed Growth Factor molecules (TGF-β)

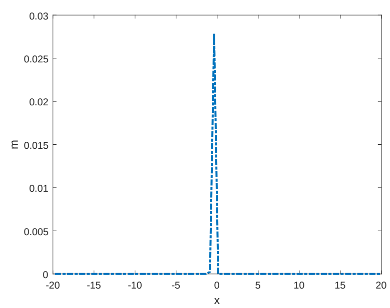
FIGURE 11. Numerical solution of the system in (2) with delay=5 for $L > T$ at $t = 25$.



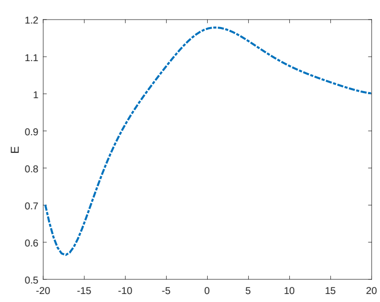
(a) Behaviour of Transformed Epithelial cells (TECs)



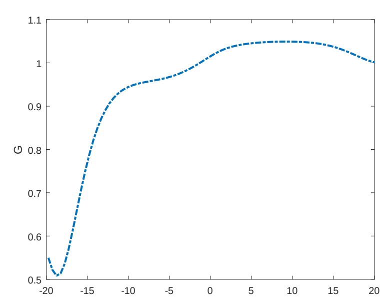
(b) Behaviour of Fibroblasts cells



(c) Behaviour of Myfibroblasts cells



(d) Behaviour of the concentration of Epidermal Growth Factor molecules (EGF)



(e) Behaviour of the concentration of Transformed Growth Factor molecules (TGF-β)

FIGURE 12. Numerical solution of the system in (2) with delay=20 for $L > T$ at $t = 25$.