Journal of the Nigerian Association of Mathematical Physics
Volume 14 (May, 2009), pp 267 – 282

Hopf bifurcations in a fractional reaction–diffusion model for the invasion and development of tumor

[1]T. A. Atabong and [2]M. O. Oyesanya
[1]*Department of Mathematics and Computer Science,*
Madonna University Elele Campus,
P. O. Box 48, Elele, Rivers State, Nigeria
[2]*Department of Mathematics,*
University of Nigeria, Nsukka.

Abstract

The phenomenon of hopf bifurcation has been well-studied and applied to many physical situations to explain behaviour of solutions resulting from differential and partial differential equations. This phenomenon is applied to a fractional reaction diffusion model for tumor invasion and development. The result suggests that more complex hopf bifurcation phenomena are possible when the complexity of the reaction and interaction increases. Results are discussed not only for fractional reaction diffusion equations, but also for ordinary differential equations and standard reaction diffusion equations as well. As a matter of fact, we demonstrated that the reaction-diffusion system portray interesting hopf bifurcation as the complexity of the equation changes. Just to say, a single equation will show hopf bifurcation of lesser complexity than those of a system of equations. The target model is the fractional reaction diffusion model for tumor invasion, conceived and analysed in situ. A uniform hopf bifurcation where the spatial and temporal sub critical and supercritical hopf bifurcations coincide is discussed for this model in a numerical simulation.

Keywords
Hopf bifurcation, tumor, fractional reaction diffusion equations

1.0 Introduction

Reaction–diffusion equations can be seen as one of the leading system of equations in the field of mathematical modeling where meritorious works have been done. It is seen extensively in population dynamics, chemical kinetics, morphogenesis and Electromagnetic theory to name a few.

Current researchers in applied mathematics are adding a diffusion term into most of their ordinary differential equations models as well as partial differential equations models to study the effects of spatial migration (see for example, Guidotti and Merino, [1];Chien and Chen, [2]). This addition is very reasonable, since most often; diffusion brings in a coupling effect to a model. This coupling is usually due to interaction and movements between the reacting components (Steen and Davis, [3]). A research on these equations is imperative because it is going to help in the explanation of physical occurrences in biological, chemical, health, economics and social sciences.

[1]Corresponding author:
[1]Telephone: 07035085016

One of the phenomena which have been the subject of many recent publications in the field of applied mathematics is hopf bifurcation. It has been applied to business, Jianpian, [4], multiparty politics, Combustion, Growth and many other areas (see for example, (Boldrin, [5]; Kalecki, [6]; Khan, 2000[7]; Marsdem and Mckracken, [8]). In the formation and development of tumor, a knowledge of bifurcation in particular and hopf bifurcation in general is necessary for physicians to understand the immediate outcome expected once parameters such as drugs, nutritional habit, physical activities, blood flow and others are changed. For example, if it is known that the carbohydrate intake is a bifurcating parameter, a slight change in this parameter will lead to multiple responses which may be positive or negative in the state of the tumor patient. Reaction diffusion equations are being classified into two categories in current research; the standard reaction diffusion equation and the fractional reaction diffusion equations. Each of these systems has been successfully used for mathematical models and other phenomenon. While some researchers have demonstrated that the standard reaction diffusion equation portrays hopf bifurcation using particular reaction, the fractional reaction systems is still lacking. We will therefore show that the reaction-diffusion system demonstrate interesting hopf bifurcation as the complexity of the equation changes. The target model is the fractional reaction diffusion model for tumor invasion, conceived and analysed analytically and numerically in the present paper.

2.0 The model

Mandelbrot and Van Ness [9] used fractional integrals to formulate fractal processes such as fractional Brownian motion. Modifications of standard equations governing physical processes such as diffusion equations, wave equation and Fokker-Planck equations which incorporate fractional derivatives with respect to time have been suggested (Vicsek, [10];Giona and Roman [11], Wyss,[12]; Schneider and Wyss, [13]; Jumaire, [14]). A fractional diffusion equation has been proposed for the diffusion on fractals. Giona and Roman [11] has shown a connection between fractional calculus and fractal structures or fractal processes. These inform our formulation in fractional diffusion equations. The model which was proposed and developed in Oyesanya and Atabong [15] is thus:

$$\frac{\partial N_c}{\partial t} = r_N N_c\left(1 - \frac{N_c}{K_N} - a_M\,\frac{M_c}{K_M}\right) - d_l L_c N_c + \frac{\partial^\alpha}{\partial x^\alpha}\left(D_{NM}\,\frac{\partial N_c}{\partial x}\right) \tag{2.1}$$

$$\frac{\partial M_c}{\partial t} = r_M M_c\left(1 - \frac{M_c}{K_M} - a_N\,\frac{N_c}{K_N}\right) + \frac{\partial^\alpha}{\partial x^\alpha}\left(D_{MN}\,\frac{\partial M_c}{\partial x}\right) \tag{2.2}$$

$$\frac{\partial L_c}{\partial t} = r_{lM} M_c - d_c L_c + r_{lN} L_c N_c + \frac{\partial^\alpha}{\partial x^\alpha}\left(D_l\,\frac{\partial L_c}{\partial x}\right) \tag{2.3}$$

where, D_{MN} and D_{NM} are defined by;

$$D_{MN} = D_m\left(1 - \frac{M_c}{K_M} - \frac{N_c}{K_N}\right), D_{NM} = D_n\left(1 - \frac{N_c}{K_N} - \frac{M_c}{K_M}\right) \tag{2.4}$$

and $0<\alpha<1$ is the fraction of diffusion of the cells and the acid in the living organism around the tumor area. These are so defined because in the absence of the tumor cells the normal cells will diffuse to occupy the space which was occupied by the tumor in a logistic growth manner. The same is true for the diffusion of tumor in the absence of normal cells.

2.1 Proposition (Non Dimensionalisation)

Let,
$$u = \frac{N_c}{K_N}, \quad v = \frac{M_c}{K_M}, \quad c = \frac{L_c}{L_0}, \tag{2.5}$$

$$L_0 = \frac{r_{lM} K_M}{d_l}, \quad \tau = r_N t, \quad \delta = \frac{r_{lM} d_l K_M}{r_N d_c}, \quad \delta_1 = \frac{d_c}{r_N}, \quad \delta_2 = \frac{r_{lN} K_N}{r_N}$$

$$\rho = \frac{r_M}{r_N}, \quad \xi = \left(\frac{r_N}{D_l}\right)^{1/\beta} x, \quad \beta = 1+\alpha, \quad d_2 = \frac{D_M}{D_l}, \quad d_1 = \frac{D_N}{D_l}. \tag{2.6}$$

Then (also see Baeumer *et al*, [30]; Baeumer *et al*, [31]; Oldham and Spanier, [32]; and Metzler and Klafter, [33]) equations (2.1), (2.2) and (2.3) become;

$$D_\tau^1 u = u(1-u-a_{12}v) - \delta cu + d_1\left(-D_\varsigma^{\beta-1}uD_\varsigma^1 u - D_\varsigma^{\beta-1}vD_\varsigma^1 u + (1-u-v)D_\varsigma^\beta u\right) \tag{2.7}$$

$$D_\tau^1 v = \rho v(1-v-a_{21}u) + d_2\left(-D_\varsigma^{\beta-1}vD_\varsigma^1 v - D_\varsigma^{\beta-1}uD_\varsigma^1 v + (1-u-v)D_\varsigma^\beta v\right) \tag{2.8}$$

$$D_\tau^1 c = \delta_1 v(v-c) - \delta_2 cu + D_\varsigma^\beta c \tag{2.9}$$

where we have used the notation $$D_\varsigma^\beta = \frac{\partial^\beta}{\partial \xi^\beta}, \qquad 2.10)$$

Proof

(see Oyesanya and Atabong, [15] for details).

3.0 Bifurcations and hopf bifurcations

***Definition* 3.1**

Let $\dfrac{du}{d\xi} = f(u,\alpha),\ \alpha \in \Re$ and F smooth. Suppose that for any sufficiently small $|\alpha|$ the system has a family of steady states $x^0(\alpha)$. Further suppose that the Jacobian matrix $A(\alpha) = f_x(x^0(\alpha),\alpha)$ has one pair of complex eigenvalues that becomes purely imaginary (of the form $\omega i,\ \omega \in \Re$), then as α passes through the real line, the equilibrium changes stability and unique limit cycles bifurcates from it and this is termed hopf bifurcation Yuri, [16].

***Remark* 3.1**

For the bifurcations on Reaction diffusion equations, see Ngwa and Maini, [17]; Chien and Chen, [2]; Guidotti and Merino, [1]. As will be seen, in its most simplified form, bifurcating solution could emerge in a reaction diffusion equation model. We shall consider the equations (2.6), (2.7) and (2.8) in different forms and examine the resulting equation for hopf bifurcation. We shall consider these equation first as ODE, then RDE and system of RDEs and system of RDEs with delay and finally as itself.

3.2 As ordinary differential equation.

Consider as a special scaling (2.1) in the absence of the tumor and the acid and as a function of time only, then, we get the ODE of the form,

$$\frac{du}{dt} = u(bu - \lambda) \tag{3.2}$$

where, λ in this case is the constant death rate of normal cell and *b* the growth rate.

The equation (3.2) has been applied to model many growth phenomena including the human growth where the births rate out weighs the death rate. A constant fraction of the population is removed all the time. Clearly, in the absence of non-linearity,

$$\frac{du}{dt} = -\lambda u \tag{3.3}$$

$\lambda = 0$ is clearly a bifurcation point since, if $\lambda > 0$ solution of equation (3.3) is stable while if

$\lambda < 0$ then the solution is unstable. If λ is complex and simple (i.e. if $\lambda = \pm i$), then the trivial solution is oscillatory (periodic) with period 2π. The fact that this parameter can be complex and simple shows that, the system 1.3 can exhibit hopf bifurcation.

3.3 As a reaction diffusion equation (RDE)

The simplest form of RDE which could be obtained from (2.6) by slight modification of parameters is;

$$\begin{aligned}&\frac{\partial u}{\partial t} = d\frac{\partial^2 u}{\partial x^2} + \lambda f(u)\ in\ \Omega\\ &u(0,t) = u_0(t),\ u(L,t) = u_L(t),\ t > 0\ on\ \partial\Omega\\ &u(x,0) = u_0(x),\ at\ t = 0\ in\ \Omega\end{aligned} \tag{3.5}$$

where d is called the diffusion coefficient, Ω the domain (the invasive region) and $\partial\Omega$ the boundary. The equation can also be obtained as a special scaling of (2.1) for only the normal cells. In a well stirred situation, we may have,

$u(0,t) = 0,\ u(L,t) = 0,\ t > 0\ on\ \partial\Omega$ and $\dfrac{\partial^2 u}{\partial t^2}$ =0 or *d=0*. The equation becomes an ODE similar to the one we already treated.

In the unevenly distribution case, we study the effects of *d* in addition to the parameter λ.

(a) Suppose u=0 is an unstable trivial solution of the ODE, then suppose that the instability is a result of the fact that,

$$f(0) = 0 \text{ and } f^{'}(0) < 0 \tag{3.6}$$

Set $\varepsilon = \dfrac{x}{L}$ in (1.5) so that we get,

$$\begin{aligned}&\frac{\partial u}{\partial t} = \frac{d}{L^2}\frac{\partial^2 u}{\partial \varepsilon^2} + \lambda f(u)\ in\ ]0,1[\\ &u(0,t) = u_0(t),\ u(1,t) = u_1(t),\ t > 0\ on\ \{0,1\}\\ &u(\varepsilon L,0) = u_0(\varepsilon),\ at\ t = 0\ in\ ]0,1[\end{aligned} \tag{3.7}$$

If the consider homogenous boundary conditions, $u(0,t) = 0,\ u(1,t) = 0,\ t > 0\ on\ \{0,1\}$ indicating a situation where no movement is permitted on the boundary, and the diffusion equals the square of the length of the domain, then we get,

$$u_t = u_{\varepsilon\varepsilon} - \lambda f(u) \tag{3.8}$$

where $u_t \equiv \dfrac{\partial u}{\partial t}$ and $u_{\varepsilon\varepsilon} \equiv \dfrac{\partial^2 u}{\partial \varepsilon^2}$ and $d = L^2$. We expand (3.8) in a Taylor series and eliminate second and higher order terms to get,

$$u_{\varepsilon\varepsilon} - \lambda f^{'}(0)u = 0 \tag{3.9}$$

Solutions of (3.9) satisfying the homogenous boundary conditions of (3.7) is in the form,

$$u = a_0 e^{-n\pi\varepsilon} \qquad 3.10)$$

Substituting (3.10) in (3.9) gives,

$$(n\pi)^2 e^{-n\pi\varepsilon} - \lambda f^{'}(0)e^{-n\pi\varepsilon} = 0. \tag{3.11}$$

Hence, $\lambda = \dfrac{n^2\pi^2}{f^{'}(0)}$, n=1, 2, 3, 4, … . For n=1, if $\lambda < \dfrac{\pi^2}{\left|f^{'}(0)\right|}$, then all the eigenvalues of the scalar system are positive showing that the unstable trivial solution is now stable due to diffusion. Similarly, we can start with a stable solution and get a condition for which instability can occur. Since the presence of diffusion has destabilized the stable steady state, we conclude that diffusion plays and important role in the phenomenon of hopf bifurcation in RD systems.

3.4 As a system of reaction-diffusion equation (RDEs)

The Brusselator, is the simplest system of equation which could be obtained from the generalised fractional system (2.6, 2.7) with the modification of some of the variables and scaling parameters of (2.1) and (2.2). It is a simple consistent model of chemical kinetics which exhibits an oscillatory behaviour. The equations are given by,

$$\left.\begin{aligned}\frac{\partial u}{\partial t} &= D_1\frac{\partial^2 u}{\partial x^2} + u^2 v - (b+1)u + a\\ \frac{\partial v}{\partial t} &= D_2\frac{\partial^2 u}{\partial x^2} - u^2 v + bu\end{aligned}\right\} \text{ in } \Omega, t>0. \tag{3.12}$$

and

$$\left.\begin{aligned}u(0,t) = u(l,t) = a\\ v(0,t) = v(l,t) = b/a\end{aligned}\right\} on\ \{0,l\} \tag{3.13}$$

In the absence of diffusion, the steady states of this system is given by,
$u = a, v = b/a$ which are the functional values on the boundary. Thus the non-trivial solution of the ODE is the trivial solution of the pde.
If we define the functions,

$$\begin{aligned}f(u,v) &= u^2 v - (b+1)u + a\\ g(u,v) &= -u^2 v + bu\end{aligned} \tag{3.14}$$

then the Jacobian of the system 3.12 can be written as,

$$\begin{pmatrix} b-1 & a^2\\ -b & -a^2\end{pmatrix}. \tag{3.15}$$

The eigenvalues of the system are given by,

$$\lambda = \frac{-(a^2-b+1) \pm \sqrt{a^4 + (b-1)^2 - 2a^2(b+1)}}{2} \tag{3.16}$$

For stability,

$$\begin{aligned}&\operatorname{Re}\lambda < 0,\\ &a^2 - b + 1 > 0 \Rightarrow a^2 + 1 > b\end{aligned} \tag{3.17}$$

For hopf bifurcation,

$$\operatorname{Re}\lambda = 0 \ and \ a^4 + (B-1)^2 - 2a^2(b+1) < 0 \Leftrightarrow a^4 + b^2 - 2b + 1 - 2a^2 b - 2a^2 < 0 \tag{3.18}$$

$$\Leftrightarrow b^2 - 2(1+a^2)b + a^4 - 2a^2 < 0 \tag{3.19}$$

b is real iff on $\sqrt{4(1+a^2) + 4(2a^2 - a^4)} \in \Re$ iff $a^2 < 2$ (3.20)

We assume that (3.20) holds and let, $\Lambda = \sqrt{4(1+a^2)^2 + 4z}$, $z = 2a^2 - a^4 > 0$. Simplification shows that $\Lambda = 2\sqrt{4a^2+1}$. For (3.19) to hold, $b \in (1 + a^2 - \Lambda/2, 1 + a^2 + \Lambda/2)$ and $a^2 < 2$.

We have therefore showed that, the non-trivial solution of the ODE is stable iff $b < 1 + a^2$.
Equally, this stability can change to instability and in this case a hopf bifurcation phenomenon can occur provided that b satisfy the following condition, $1 + a^2 - \Lambda/2 < b < 1 + a^2 + \Lambda/2$.
Thus the change in stability is accompanied by a hopf bifurcation. Realised that the hopf bifurcation is coming as a result of the non-linearity in the model and to some extent it can be linked to the coupling effect of the model.

We now show that if $b < 1 + a^2$, the full reaction diffusion system (3.12) shows a different stability and hopf bifurcation conditions. We analysed stability based on the perturbed states $M = u - a, N = v - \frac{b}{a}$.
Substituting in (3.12) gives,

$$\left.\begin{aligned} \frac{\partial M}{\partial t} &= D_1 \frac{\partial^2 M}{\partial x^2} + (M+a)^2 (\frac{N+b}{a}) - (b+1)(M+a) + a \\ \frac{\partial N}{\partial t} &= D_1 \frac{\partial^2 N}{\partial x^2} + (M+a)^2 (\frac{N+b}{a}) + b(M+a) \end{aligned}\right\} \tag{3.21}$$

The boundary conditions will be, $M(0,t) = M(1,t) = N(0,t) = N(1,t) = 0$. Without loss of generality, we replace the variables {*M*, *N*} with {*u*, *v*} for the sake of convenience.
Hence we have,

$$\left.\begin{aligned} \frac{\partial u}{\partial t} &= D_1 \frac{\partial^2 u}{\partial x^2} + (b-1)u + a^2 v + u^2 v + \frac{b}{a} u^2 + 2auv \\ \frac{\partial v}{\partial t} &= D_2 \frac{\partial^2 v}{\partial x^2} + bu - a^2 v - (u^2 v + \frac{b}{a} u^2 + 2auv) \end{aligned}\right\} \tag{3.22}$$

$$\Leftrightarrow \frac{\partial}{\partial t}\begin{pmatrix} u \\ v \end{pmatrix} = \begin{pmatrix} D_1 & 0 \\ 0 & D_2 \end{pmatrix} \frac{\partial^2}{\partial x}\begin{pmatrix} u \\ v \end{pmatrix} + \begin{pmatrix} b-1 & a^2 \\ -b & -a^2 \end{pmatrix}\begin{pmatrix} u \\ v \end{pmatrix} + \begin{pmatrix} u^2 + \frac{b}{a}u^2 + 2auv \\ -u^2 - \frac{b}{a}u^2 - 2auv \end{pmatrix} \tag{3.23}$$

Solutions satisfying the boundary conditions of the perturbed system (3.21) are of the form,

$$\begin{pmatrix} u \\ v \end{pmatrix} = \begin{pmatrix} c_1 \sin(\frac{k\pi x}{l}) \\ c_2 \sin(\frac{k\pi x}{l}) \end{pmatrix} \tag{3.24}$$

Substituting (3.24) into (3.23) and taking the determinant gives,

$$\left| \begin{pmatrix} \left(\frac{k\pi}{l}\right)^2 D_1 - (b-1) & -a^2 \\ b & \left(\frac{k\pi}{l}\right)^2 D_2 + a^2 \end{pmatrix} \right| = 0 \tag{3.25}$$

Let *T* be the matrix represented by (3.25)
The determinant and trace of T are given respectively as,

$$Det(T) = \left(\left(\frac{k\pi}{l}\right)^2 D_1 - (b-1) \right)\left(\left(\frac{k\pi}{l}\right)^2 D_2 + a^2 \right) + a^2 b \tag{3.26}$$

$$Trace(T) = \left(\frac{k\pi}{l}\right)^2 D_1 - (b-1) + \left(\frac{k\pi}{l}\right)^2 D_2 + a^2$$

The presence of a negative sign in (3.26) affecting both the trace and the determinant shows that these quantities can vanish at some value of the parameters.

First, the trace changes sign at $b = 1 + a^2 + \frac{\pi^2 k^2}{l^2}(D_1 + D_2)$ showing that we can have stability or instability depending on the determinant.

If we supposed that the determinant is greater than zero, then a negative trace indicates that, there exist two positive values for the eigenvalues in which case we have instability. Thus the region of stability and instability shall exist immediately the determinant is negative.
Note that, $Det(T)=0$ iff,

$$b = 1 + \left(\frac{k\pi}{l}\right)^2 D_1 + \frac{D_1}{D_2}a^2 + \frac{a^2}{D_2}\left(\frac{l}{k\pi}\right)^2 \qquad (3.27)$$

We denote this value of b as b_s. If $b > b_s$ then as mentioned above, one of the eigenvalue is negative and the other is positive. The existence of a positive and negative eigenvalues is an indication that the reaction diffusion system (3.21) having the trivial solution $(u,v)=(0,0)$ loses stability. In original variables this is similar in saying that $(u,v)=(a,b/a)$ loses stability at $b>b_s$. From the choice of an eigen function, there exist a different b_s for each k and call these b_s as b_{sk} ($k = 1,2,3,\ldots$) and let us denote the minimum of these b_{sk} by $b`$ then, $b` = \min_k b_{sk}$. It follows that, the minimum of b_{sk} is given by,

$$b` = 1 + \frac{D_1}{D_2}a^2 + 2a\sqrt{\frac{D_1}{D_2}} \qquad (3.28)$$

This is obtained by differentiating (3.27) w.r.t. k and finding the minimum of such k following our normal techniques from calculus.

3.4.1 Claim

There exist a value of D_1D_2, such that $b` < 1+a^2$. See that,

$$1 + \frac{D_1}{D_2}a^2 + 2a\sqrt{\frac{D_1}{D_2}} < 1 + a^2 \Leftrightarrow \left(\frac{D_1}{D_2} - 1\right)a + 2\sqrt{\frac{D_1}{D_2}} < 0 \qquad (3.29)$$

$\Leftrightarrow a < 2\sqrt{\frac{D_1}{D_2}}\left(1 - \frac{D_1}{D_2}\right)^{-1}$ and $D_1 < D_2$. If D_2 is very large, we have instability. Equation (3.29) gives us the conditions under which this instability from the stable steady state of the ODE can occur in the presence of diffusion.

We assume that $b = 1 + a^2$ is the bifurcating point since at this point stability changes.
A hopf bifurcation will occur in the system in case, $trace(T)=0$ and $det(T)>0$.
This is true iff,

$$a^2 > \frac{D_1\left(\frac{k\pi}{l}\right)^2}{\sqrt{\left[\left(\frac{k\pi}{l}\right)^2(D_1 + D_2) - \frac{D_1}{D_2} - \frac{1}{D_2}\left(\frac{l}{k\pi}\right)^2\right]}} \quad \text{and} \quad D_1 > \frac{\frac{1}{D_1}\left[\left(\frac{l}{k\pi}\right)^2 - \left(\frac{k\pi}{l}\right)^2 D_2\right]}{\left(\left(\frac{k\pi}{l}\right)^2 - \frac{1}{D_1}\right)} \quad \text{and} \quad D_2 > \left(\frac{l}{k\pi}\right)^2$$

These conditions must be satisfied before a hopf bifurcation can occur. It is possible to get the smallest possible value of k for which this hopf bifurcation can occur.

3.5 As a class of delay reaction-diffusion system (RDEs with delay).

Generally we incorporate delay in a reaction –diffusion equation in order to obtain the behaviour of the system at a future state as a consequence of the behaviour of past state. Delay reaction–diffusion system have been considered in population models by various researchers (Al-omari and Gourley, [18]; Tang and Li-Zhou, [19]; Gourley and Bartuccelli, [20]). Fedotov and Lomin [21] recently worked on delay reaction diffusion model for tumor invasion. Considering hopf bifurcation in a delay model is of importance in the fight against tumor invasion. Knowing the history of a patient is always a significant decision to be made by a doctor for any diagnosis and prescriptions. Accordingly, a bifurcation parameter may be of paramount importance to the previous history of the patient.

Consider reaction functions satisfying the equation (as in Tang and Li-Zhou, [19]),

$$\begin{aligned}\frac{\partial u}{\partial t} &= d_1\frac{\partial^2 u}{\partial x^2} + r_1 u\left[1 - \int_{-\infty}^{t} f(t-\tau)u(r,x)d\tau - \mu\int_{-\infty}^{t} f(t-\tau)v(\tau,x)d\tau\right]\\ \frac{\partial u}{\partial t} &= d_2\frac{\partial^2 u}{\partial x^2} + r_2 u\left[1 - \int_{-\infty}^{t} f(t-\tau)u(r,x)d\tau - \mu\int_{-\infty}^{t} f(t-\tau)v(\tau,x)d\tau\right]\end{aligned} \qquad (3.30)$$

where, μ_1, μ_2, r_1, r_2 are real numbers such that, $\mu_1 < 1 < \frac{1}{\mu_2}$ (3.31)

where, I: $f(x,t) \ge 0$, $(x,t) \in (-\infty,+\infty)X[0,+\infty)$.

II: $\forall t > 0$, f is an even function of *x*.

III: $\int_{-\infty}^{+\infty}\int_{0}^{+\infty} f(x,t)dtdx = 1, \ i, j = 1,2,3...$

With the condition (3.31), we shall have at least one positive steady state of (3.30). Since in development of tumor we have competition between, the normal and the tumor cells, we can consider the memory function of the form $f(t) = \alpha e^{-\alpha t}$ also called the weak generic kernel. The uniform steady state of (3.30) is $(u^*, v^*) = \left(\frac{1-\mu_1}{1-\mu_1\mu_2}, \frac{1-\mu_2}{1-\mu_1\mu_2}\right)$. Using the boundary conditions,

$$\frac{\partial u}{\partial n} = \frac{\partial v}{\partial n} = 0 \quad t \in \Re, \cdots x \in \partial\Omega \qquad (3.32)$$

$(u,v) = (\varphi_1(t,x), \varphi_2(t,x)), (t,x) \in (-\infty,0]X\overline{\Omega}$ where, $\Omega \in \Re^n$ is bounded.

We linearize (3.30) and simplify accordingly using the generic kernel $f_\alpha(s) = \frac{s}{\alpha^2}e^{-s/\alpha}$, $\int_{-\infty}^{0} f_\alpha(-s)e^{\lambda s}ds = \frac{1}{(1+\lambda\alpha)^2}$, and get the determinant of the characteristic equation has the form,

$$\left[(\lambda + v_n)(\alpha^2\lambda^2 + 2\lambda\alpha + 1) + M_1\right]\left[(\lambda + v_n)(\alpha^2\lambda^2 + 2\lambda\alpha + 1) + M_2\right] = 0 \qquad (3.33)$$

$n = 0, 1, 2, \ldots$

For $n = 0$, the equation (3.33) has roots of the form, $\frac{i}{\alpha_0}, -\frac{i}{\alpha_0}$ and $-2\frac{i}{\alpha_0}$ and for any other n, all roots have negative real part. The fact that we have simple complex eigenvalues is an indication that $\alpha = \alpha_0$ is a bifurcation point and a hopf bifurcation actually occurs in the neighbourhood of this point. In particular, for values of $\alpha \ge \alpha_0$, there exist some spatio-temporal patterns in this region. Since the delay was considered in time and not in space, a more exciting phenomenon of hopf bifurcation will surface at very simple conditions, if the migration to current location was influenced by previous migration location. This is a subject to consider for further research.

4.0 As a fractional reaction diffusion equations

4.1 Existence and stability of equilibrium solutions

Table 4.1 below, shows the equilibrium points obtained from (7-9) (Oyesanya and Atabong, [15])

Table 4.1: Possible Equilibrium State

Code	Normal cells (u)	Tumor cells (v)	H^+ Conc(c)	Description
ES1	0	0	0	Trivial Steady State. No cells population
ES2	0	1	1	Death Equilibrium
ES3	k^*	$1-a_{12}k^*$	$b_1-b_2k^*$	Both populations are existing in a low pH
ES4	1	0	0	Disease free Equilibrium
ES5	δ_1/δ_2	0	1	Attack Stage of the disease
ES6	$1-\delta$	$1+\delta_2(\delta-1)$	1	Normal cells are been crushed to the credit of the tumor cells.ES3 is going to ES6

Earlier result predicts that;

(1) If $a_{12} > 1$, $\delta_1 < \delta_2$ and $a_{21} < 1$, there exist at least one non-zero steady state where the normal and tumor cells are surfing in the acidic microenvironment provided $a_{12}a_{21} > 1$ (The tumor death hypothesis).

(2) It is possible to get a change in stability (Hopf bifurcation) if $\delta_1 < 1$.

(3) The steady states ES2 and ES4 (see Table 1) are all stable.

We will now proceed to obtain the critical parameter values for which ES2 and ES4 are approached from ES3 in a perturbation analysis.

4.2 Fractional analysis

As a means of simplification, we considered a situation where both normal and tumor tissues are well regulated and participate normally in an organ and will therefore not be diffusing in space as a result of the tumor cells. Under these same assumptions, and in addition, the cells are diffusing at a constant rate D_1 for normal cells, D_2 for tumor cells and D_3 for H^+. With these assumptions, all mixed order fractional spatial derivatives are zero and equation (2.7) - (2.9) become,

$$\begin{aligned} D_\tau^1 u &= u(1-u-a_{12}v) - \delta cu + d_1\left(D_\varsigma^\beta u\right) \\ D_\tau^1 v &= \rho v(1-v-a_{21}u) + d_2\left(D_\varsigma^\beta v\right) \\ D_\tau^1 c &= \delta_1 v(v-c) - \delta_2 cu + D_\varsigma^\beta c \end{aligned} \tag{4.1}$$

In equation (4.1) we set,

$$f(u,v,c) \equiv u(1-u-a_{12}v) - \delta cu;\ g(u,v,c) \equiv \rho v(1-a_{21}u-v);\ h(u,v,c) \equiv \delta_1(v-c) + \delta_2 cu \tag{4.2}$$

and study the linearization about the steady states (u^*, v^*, c^*), by expansion in a Taylor series and retaining only linear terms to get the operator equation,

$$LU = KU\ , \tag{4.3}$$

where,

$$L = \begin{pmatrix} D_\tau^1 - d_1 D_\varsigma^\beta & 0 & 0 \\ 0 & D_\tau^1 - d_2 D_\varsigma^\beta & 0 \\ 0 & 0 & D_\tau^1 - D_\varsigma^\beta \end{pmatrix}, \quad K = \begin{pmatrix} f_u(U^*) & f_v(U^*) & f_c(U^*) \\ g_u(U^*) & g_v(U^*) & g_c(U^*) \\ h_u(U^*) & h_v(U^*) & h_c(U^*) \end{pmatrix}$$

$$U = (u, v, c)^T, \quad U^* = \left(u^*, v^*, c^*\right)$$

Seek for solution of (4.3) in the form $U = e^{\theta\tau} e^{\sigma i \varsigma}$ and substitute in equation (4.3) to get,

$$\begin{pmatrix} \theta - d_1(\sigma i)^\beta & 0 & 0 \\ 0 & \theta - d_2(\sigma i)^\beta & 0 \\ 0 & 0 & \theta - (\sigma i)^\beta \end{pmatrix} + \begin{pmatrix} f_u(U^*) & f_v(U^*) & f_c(U^*) \\ g_u(U^*) & g_v(U^*) & g_c(U^*) \\ h_u(U^*) & h_v(U^*) & h_c(U^*) \end{pmatrix} = 0 \qquad (4.4)$$

We have used the fact that the fractional derivatives of the exponential is generally given by, $D^\beta e^{ax} = a^\beta e^{ax}$, (Podlubny, [22] ; Erdelyi *et al.*, [23]; Meerschaert *et al.*, [24];Miller and Ross, [25]). Stability of operator equation (4.3) is determined by the matrix given by,

$$A = \begin{pmatrix} \theta - d_1(\sigma i)^\beta - f_u(U^*) & -f_v(U^*) & -f_c(U^*) \\ -g_u(U^*) & \theta - d_2(\sigma i)^\beta - g_v(U^*) & -g_c(U^*) \\ -h_u(U^*) & -h_v(U^*) & \theta - (\sigma i)^\beta - h_c(U^*) \end{pmatrix}$$

The dispersion relation of the operator equation using the matrix A is given by,

$$\lambda^2 - TraceA + DetA, \text{ where } TraceA = 3\theta - (1 + d_1 + d_2)(\sigma i)^\beta - (f_u + g_v + h_c)$$

$$DetA = \left(\theta - d_1(\sigma i)^\beta - f_u\right)\left[\left(\theta - d_2(\sigma i)^\beta - g_v\right)\left(\theta - (\sigma i)^\beta - h_c\right) - g_c h_v\right] +$$
$$f_v\left[-g_v\left(\theta - (\sigma i)^\beta - h_c\right) - g_c h_u\right] - f_c\left[g_u h_v + h_c\left(\theta - d_2(\sigma i)^\beta - g_v\right)\right]$$

Setting $\beta = 2$ in *Trace A* and simplifying for bifurcation, we obtain the relationship,

$$3\theta(\sigma) = -\sigma^2(1 + d_1 + d_2) + (f_u + g_v + h_c), \qquad (4.5)$$

which is the three components relationship corresponding to what was obtained by Marc for the two components ordinary reaction diffusion equation Marc, [26]. A similar relationship is obtained for the determinant given by,

$$DetA = \theta^3 - \theta^2\chi - \theta^2 h_c + \theta d_1 d_2 \chi^2 - d_1 d_2 \chi^3 - d_1 d_2 \chi^2 h_c + \theta d_1 \chi g_v - d_1 \chi^2 g_v +$$
$$-d_1 \chi g_v h_c - \theta^2 d_1 \chi + \theta d_1 \chi^2 + \theta d_1 \chi h_c - \theta^2 d_2 \chi + \theta d_2 \chi^2 + \theta d_2 \chi h_c - \theta^2 g_v + \theta \chi g_v + \theta g_v h_c +$$
$$-\theta^2 f_u + \theta \chi f_u + \theta f_u h_c + \theta d_2 \chi f_u - d_2 \chi^2 f_u - d_2 \chi f_u h_c + \theta f_u g_v - \chi f_u g_v - f_u g_v h_c - \theta g_c h_v + d_1 \chi g_c h_v +$$
$$+ f_u g_c h_v - \theta f_v g_v + \chi f_v g_v + f_v g_v h_c - f_v g_c h_u - f_c g_u h_v - \theta f_c h_u + d_2 \chi f_c h_u + f_c g_v h_u$$

where, $\chi = (\sigma i)^\beta$. If $\beta = 2$ $\chi = -\sigma^2$ and the relation of the determinant becomes (See Oyesanya and Atabong, [15]),

$$DetA = d_1 d_2 \sigma^6 + \sigma^4(\theta d_1 d_2 + \theta d_1 + \theta d_2 - d_2 f_u - d_1 g_v)$$
$$+ \sigma^2 \begin{pmatrix} \theta^2 + d_1 g_v h_c + \theta^2 d_2 + \theta^2 d_1 + d_2 f_u h_c + f_u g_v - d_1 d_2 h_c - \theta d_1 g_v - \theta d_1 h_c - \theta d_2 h_c - \theta g_v + \\ -\theta f_u - \theta d_2 f_u - d_1 g_c h_v - f_v g_v - d_2 f_c h_u \end{pmatrix}$$
$$+ \theta^3 + \theta g_v h_c + \theta f_u h_c + \theta f_u g_v + f_c g_v h_u + f_u g_c h_v + f_v g_v h_c - \theta^2 f_u - f_u g_v h_c - \theta g_c h_v - \theta f_v g_v +$$
$$- f_v g_c h_u - f_c g_u h_v - \theta f_c h_u - \theta^2 h_c - \theta^2 g_v$$

Using the value of $\beta = 2$ as shown above, one easily sees from the *TraceA* and *DetA* relations above, that the trivial steady state (0,0,0) is unstable while the other steady states depends on the choice of our parameters.

On the other hand, for $1 < \beta < 2$, the eigenvalues of the community matrix A are complex as seen from the structure of the dispersion relation showing that the solution of this linearized system are oscillatory and can exhibit bifurcation phenomenon depending on the parameters.

4.3 Discussion

A situation of Hopf bifurcation phenomenon is possible (Guidotti and Merino, [1]; Oyesanya, [27]; Margolis, [28]; Chien and Chen, [2]; Murray, [29]) in case, Trace(A) = 0 and Det(A) > 0 or Det(A) = 0 and Trace(A) < 0. Either of these conditions will guarantee simple eigenvalues for the dispersion relation given above. Starting with the first case,

$$TraceA = 3\theta - (1 + d_1 + d_2)(\sigma i)^{\beta} - (f_u + g_v + h_c) = 0$$

$$\Leftrightarrow \theta(\sigma) = \frac{(1 + d_1 + d_2)(\sigma i)^{\beta} + (f_u + g_v + h_c)}{3}$$

$$\frac{d\theta(\sigma)}{d\sigma} = \frac{\beta}{3}(1 + d_1 + d_2)(\sigma)^{\beta-1} i^{\beta}; \quad \frac{d^2\theta(\sigma)}{d\sigma^2} = \frac{\beta(\beta-1)}{3}(1 + d_1 + d_2)(\sigma)^{\beta-2} i^{\beta}$$

Since $\frac{d^2\theta(\sigma)}{d\sigma^2} < 0$, $\theta(\sigma)$ has at least a maximum value while crossing from the positive to the negative half plane. The maximum value occurs at σ =0. A sketch of the contours of $\theta(\sigma)$, for different values of the parameters can be seen below;

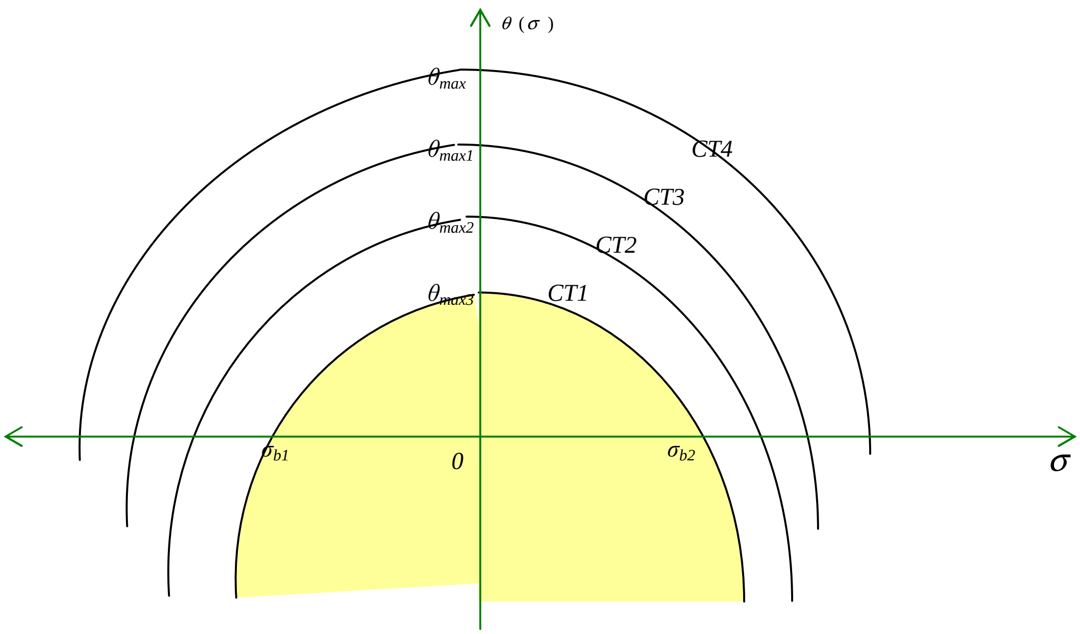


Figure 4.1: Contours of the spatial variation parameter value of the trace σ against the temporal variation θ

where, $\theta_{\max} = \frac{(f_u + g_v + h_c)}{3}$ and $-\sqrt[\beta]{\frac{-(f_u + g_v + h_c)}{(1 + d_1 + d_2)}}\, i = \sigma$.

The maximum value of the turning points on each of the contours varies as the steady states and the diffusion coefficients, d_1 and d_2 as shown above. The shaded region indicates the region of competition for survival since all solutions in this neighbourhood are unstable to small perturbation and therefore liable to change. This is seen from the fact that in this region, the spatial and temporal variation parameter fluctuates in an uncertain way. Between 0 and σ_{b2} the spatial variation is on the rise while the temporal variation is on the decline. This will make the solution to grow rapidly and as such will lead to instability. Similarly situation occurs in the negative half plane.

Outside this region, in particular, in the negative half plane, both parameters increases negatively thereby resulting to an exponential decrease in solution as a result of which the solution becomes stable. In the negative half plane on the other hand, the negative increase in space is more intense than the positive increase in time and as a result, the overall effect will be a decrease in the growth of the solution curve. Thus there will be spatial and temporal stability and any of the interacting species will surrender to the other as a matter of time. In this region for example, if $\sigma < \sigma_{b1}$ then the solution has the form, $e^{-\theta\tau}e^{-i\sigma\xi}$ which tends to zero with time and space while on the other half plane, $\sigma > \sigma_{b2}$ then the solution is of the form, $e^{-\theta\tau}e^{i\sigma\xi}$ and since spatial variation cannot go above a certain large value, the overall effect of this solution will turn to zero. There, the different steady states will give rise to different conditions of the parameters of the system. To start with, the first derivatives of these functions are given by;

$$f_u = 1 - 2u - a_{12}v - \delta c,\ f_v = -a_{12}u,\ f_c = -\delta u$$
$$g_u = -a_{21}\rho v, g_v = \rho - a_{21}\rho u - 2\rho v, g_c = 0$$
$$h_u = \delta_2 c, h_v = \delta_1, h_c = -\delta_1 + \delta_2 u$$

The Steady state ES1 will give the following derivative values computed at this steady state.

$$f_u = 1,\ f_v = 0,\ f_c = 0,\ g_u = 0, g_v = \rho, g_c = 0\ h_u = 0, h_v = \delta_1, h_c = -\delta_1.$$

These values will give $\theta_{\max} = \dfrac{(1-\delta_1+\rho)}{3}$ and since $\delta_1 < 1$, $\theta_{\max} > 0$ and our parameters will lie in the instability region which was what we had in the linear analysis of the previous work (Oyesanya and Atabong, [15]). This is supported by the fact that the spatial intercept $-\sqrt[\beta]{\dfrac{-(1-\delta_1+\rho)}{(1+d_1+d_2)}}i = \sigma$ have two values. Since $(1-\delta_1+\rho) > 0$, the value of $-(1-\delta_1+\rho)$ will be negative hence has values, in both the positive and the negative half plane therefore the shaded region as mentioned above will correspond to values of stability. The steady state ES2 will have values,

$$f_u = 1 - a_{12} - \delta,\ f_v = 0,\ f_c = 0,\ g_u = -a_{21}\rho, g_v = -\rho, g_c = 0\ h_u = \delta_2, h_v = \delta_1, h_c = -\delta_1 + \delta_2$$

$\theta_{\max} = \dfrac{(1-\delta_1-a_{12}-\rho-\delta_1+\delta_2)}{3} = \dfrac{(1-2\delta_1-a_{12}-\rho+\delta_2)}{3}$ and since $1-a_{12} < 0$, $\delta < \delta_2$ we have that this maximum value is less than zero showing that the parameters lies outside the region of instability hence this steady state must be stable. Under similar consideration, we see that the steady state ES4 is stable. Therefore, under what condition can the steady state ES3 go to ES2 or ES4? By substituting ES3 into the above null trace relationship, we get,

$$\theta_{\max} = \frac{1-2K^* - a_{12}(1-a_{12}K^*) - \delta(b_1 - b_2K^*)}{3} = \frac{1-2K^* - a_{12} + a_{12}^2K^* - \delta b_1 + \delta b_2 K^*)}{3}$$

Substituting the values for the parameters b_1 and b_2 and simplifying, we see that, for both population to exist $a_{12}a_{21} > 1$. This condition was also proved in the linear analysis of the previous work. This was obtained by setting maximum temporal parameter to zero which is logical since we have that the shaded region in the contours of figure 1 corresponds to instability. Therefore for us to have stability for this state we must reckon that this value be zero or negative. Also from this condition we see that if $a_{12} >>> a_{21} > 0$ then the Steady state

ES4 will be approached from ES3 while if $a_{21} >>> a_{12} > 0$ and $b_1 > b_2 > 0$ are of approximately the same magnitude, such that $|a_{12} - a_{21}| < \varepsilon$ no matter how small $\varepsilon > 0$ may be, then ES2 is approached from ES3. The value of $-\sqrt[\beta]{\frac{-(f_u + g_v + h_c)}{(1+d_1+d_2)}}\,i = \sigma$ in both cases will lie in the lower negative half plane.

Since we established the existence of non-zero steady state for $a_{12}a_{21} < 1$ if $a_{12} > 1$, $\delta_1 < \delta_2$ and $a_{21} < 1$, we now couple this with the above result to conclude that, only the trivial steady state exist and is unstable for any a_{12} and a_{21} satisfying the tumor death hypothesis with $a_{12}a_{21} < 1$. if the quotient of a_{12} and a_{21} is approximately one then the stability of the state ES2 prevails while if the product is by far greater than one then the disease free equilibrium prevails. The value of $\frac{a_{12}}{a_{21}} = 1$ is a multiple bifurcation point whereby if $\frac{a_{12}}{a_{21}} < 1$ we have a sub critical hopf bifurcation of the trivial solution and all other solutions. The case, $\frac{a_{12}}{a_{21}} = 1$ we have a supercritical hopf bifurcation of the ES2 solution and subcritical hopf bifurcation of the other solutions. As $\frac{a_{12}}{a_{21}} > 1$ the disease free equilibrium solution is more and more stable giving a supercritical hopf bifurcation of this solution and a corresponding sub critical hopf bifurcation to the trivial solution and the ES2 solution. Hence as the parameters vary, the stability constantly changes by shifting from one steady state to another.

4.3.1 Numerical simulations and further discussions

To concretise the prognostics discussed above, we simulate the general conditions for hopf bifurcation for which the hopf bifurcation theorem is satisfied. Table 4.2 below, gives the values of our parameters for which bifurcating solution can occur.

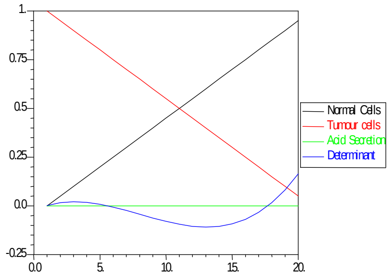
Table 4.2: Table of Parameters regimes for bifurcation

Steady State	**Parameters**	**Steady State**	**Parameters**
	*delta*2 = ss1.2, *delta*1 = 0.8		*delta*2 = 1.9,*delta*1 = 1.8
ES1	d_1 = 0.05, d_2 =1.95, a_{12} = 1.00965, a_{21} = 0.0034, *ru* = 1, *delta* = 0.67,	ES1	d_1 = 0.05, d_2 = 1.95, a_{12} = 1.00965, a_{21} = 0.0034, *ru* = 1, *delta* = 0.67,
ES2	!!	ES2	!!
ES3	!!	ES3	!!
ES4	!!	ES4	!!
ES5	!!	ES5	!!
ES6	!!	ES6	!!

A program was written in SlyverFrost FNT95 –pluto platform to obtain values which were plotted using ESPlot version 12 to obtain the curves presented below.

From Figure 4.1, we see that the cohabiting steady state exist in the absence of the acid secretion but is however unstable at all proportions of tumor–normal cells population. But in the case where the tumor is emerging, with a proportion of 0.0125 over the normal cells, then the steady state will bifurcate within the parameters regime shown in Table 4.2 for $\delta_1 < 1$.

BIFURCATION OF STEADY STATES



Fig**ure 4.2:** Variation of determinant (curve) with tumor, normal cells at 0 acid production

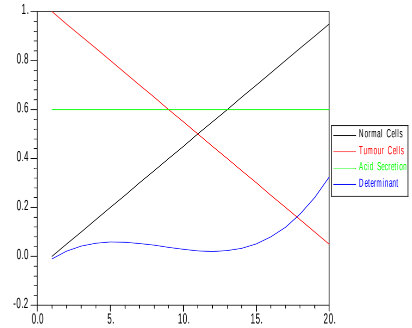


Figure 4.3: Variation of Determinant (curve) with tumor, Normal cells at 0.6 acid production

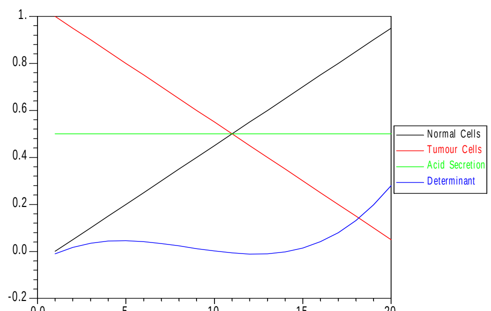


Figure 4.4: Variation of Determinant(curve) with tumor, Normal cells at 0.5 acid production

BIFURCATION OF STEADY STATES

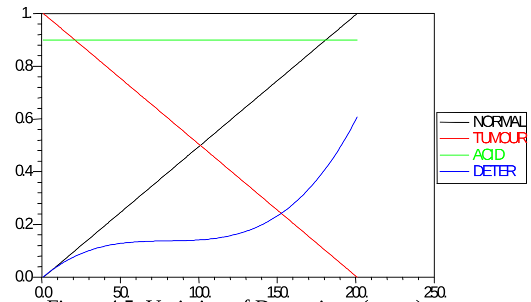


Figure 4.5: Variation of Determinant(curve) with tumor, Normal cells at 0.9 acid production

BIFURCATION OF STEADY STATES

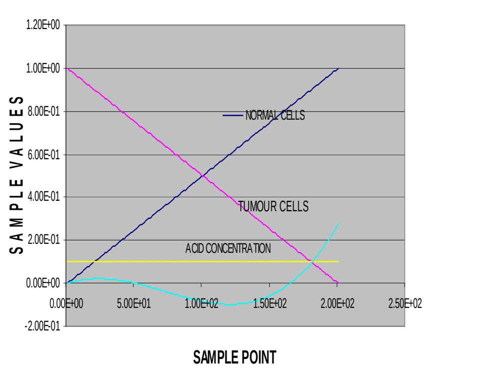


Figure 4.6: Variation of Determinant (curve) with tumor, Normal cells at 00.1 acid production.

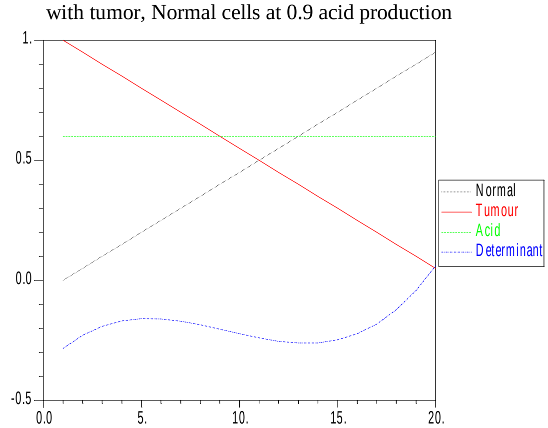


Figure 4.7: Variation of Determinant (curve) with tumor, Normal cells at 0.6 acid production for $\delta_1 > 1$.

If $\delta_1 > 1$ then no bifurcation can exist as shown in Figure 4.7. If the acid concentration increases from zero but stay within the neighbourhood of the zero, the tumor and the normal cells will both exist but this will be unstable as shown in fig5 where the determinant is negative between sample points 5.0E-01 and 1.7E-02. Above sample point 1.7E-02, the determinant is positive showing that hopf bifurcation will emerge. Figure 4.3, Figure 4.4, Figure 4.5 show slight increase in the concentration of acid in the cells which leads to hopf bifurcations of various magnitudes. Since δ_1 in original variables, is proportional to the rate of acid re-absorption (d_c) and inversely proportional to the rate of normal cell growth (r_N), $\delta_1 > 1$ is seen as more acid production rate to normal cell growth leading to spatio-temporal pattern in the development of tumor. In another way, increasing $\delta_1 > 1$ is seen as increase in the acid secretion by normal cells since $\delta_1 < \delta_2$. Fig3 shows equivalence in spatio-temporal pattern and hopf bifurcation when $\delta_1 \approx 1$. At these values, we have a situation of spatio-temporal hopf bifurcation where the rate of acid production is maintained proportional to the rate of normal cell division. This will increase δ thereby increasing the rate of secretion of acid by tumor and subsequently increasing the rate of tumor development.

5.0 Conclusion

We have analysed differential equations for hopf bifurcations. Five classes of equations were considered: The general ordinary differential equation, the reaction diffusion equation, the system of reaction diffusion equation, a system of delay reaction diffusion equation and a model for a fractional reaction diffusion model for tumor invasion. In the process, we saw that as the complexity of the equation increases, more hopf bifurcation phenomena are posible. The special case of a fractional reaction diffusion equation for tumor invasion was visited and the complexities of multiple hopf bifurcations as the bifurcation parameter changes were seen. From the bifurcation results of the fractional reaction diffusion model by simulation, we see that the way forward of eradicating tumor, is to keep $\delta_1 < 1$ by reducing the acid secretion by both normal cells and by tumor cells by increasing the rate of acid re-absorption using immunotherapeutic drugs which can increase this rate or concentrate in the elimination of this acid secretion.

References

[1] P. Guidotti and S. Merino (1997). Hopf bifurcation in a scalar reaction diffusioin equation. Jour. Diff. Equa., 140:209-222.

[2] C. S. Chien and M. H. Chen (1998). Multiple Bifurcations in a reaction-Diffusion Problem. Computer math. Appl. 35(8):15-39.

[3] P. H. Steen and S. H. Davis (1982). Quasiperiodic bifurcation in nonlinear oscillators near a point of strong resonance. SIAM J. App. Math., 42:1345-1368.

[4] C. Jianpian (2005). Hopf bifurcations in the IS-LM business cycle model with delay. Electronic jour. of differential equations, 2005(15):1-6.

[5] M. Boldrin (1984). Applying bifurcation theory: Some simple results on Keynesian business cycles, DP8403, Uni. Of Venice.

[6] M. Kalecki (1935). A microdynamics theory of business cycle. Econometrica, 3:327-344.

[7] J. A. Khan (2000). Hopf bifurcation in multiparty political systems with time delay in switching. Applied Math. Lett., 13:43-52.

[8] E. J. Marsdem and M. Mckracken (1976). The hopf bifurcation and its application. New York, Springer.

[9] B. B. Mandelbrot and N. Van (1968). Anomalous Behaviors in Fractional Fokker-Planck Equation. Siam Review 10: 422.

[10] Vicsek, T. (1989), Fractal Growth Phenomena, Singapore, World Scientific.

[11] M. Giona and H. E. Roman (1992). Path integral representation for fractional Brownian motion. Phys. A: Math. Gen. 25:2093.

[12] N. Wyss (1986). The fractional diffusion equation. J. Math. Phys. 27, 2782.

[13] W. R. Schneider and N. Wyss (1989) J. Math. Phys. 30, 134

[14] G. Jumaire (1992). J. Math. Phys. 33:3536

[15] M. O. Oyesanya and T. A. Atabong (2008), A fractional reaction diffusion model for tumor invasion, J. Nig. Math. Soc., 26:159-195.

[16] A. K. Yuri,(2007). Andronov Hopf bifurcation. Department of mathematics, Utrecht Univ. The Netherlands.

[17] G. A. Ngwa and P. K. Maini (1995). Spatio-temporal patterns in a mechanical model for mesenchymal morphogenesis.

[18] J. Al-omari and S. A. Gourley (2003). Stability and travelling fronts in Lotka-Volterra competition models with stage structure, SIAM J. Appl. Math. 63(6):2063-2086.

[19] Y. Tang and Li Zhou (2005). Hopf bifurcation and Stability of a competition diffusion system with distributed delay. Publ. RIMS, Kyoto Univ. 41:579-597.

[20] S. A. Gourley and M. V. Bartuccelli (1997). Parameter domains for instability of uniform states in system with many delays. J. Math. Biol. 35:843-867.

[21] S. Fedotov, and A. Lomin (2007). Migration and proliferation dichotomy in tumor cells invasion. Phy. Rev. lett, 98 (11): 118101-1-118101-4.

[22] I. Podlubny (2005). Fractional Derivatives: History, Theory, Applications, Logan, Utah University.

[23] A. Erdelyi, W. Magnus, F. Oberhettinger and F. G. Tricomi (1955). Higher Transcendental Functions, Vol 3. New York, Mcgraw – Hill.

[24] M. M. Meerschaert, J. Mortensen and H.P. Scheffler (2004). Vector Grunward formula for fractional derivatives. J. Frac. Cal and Appl. 10:136-143.

[25] K. S. Miller and B. Ross (1993). An Introduction to the Fractional Calculus and Fractional Differential Equations, New York, Wiley.

[26] R. R. Marc (2004). Reaction Diffusion Equation. Lecture notes on Stability Analysis.

[27] M. O. Oyesanya (2005), Symmetry and secondary bifurcation of elastic structures, Mech. Res. Comm. 32: 121-137.

[28] S. Margolis (1991). New routes to quasi-periodic combustion of solids and high-desity fluids near resonant hopf bifurcation points. SIAM J. of App. Math. 31(3):693-726.

[29] D. Murray (2003). Mathematical Biology, Berlin, Springer-Verlag.

[30] B. Baeumer, M. Kovacs and M. M. Meerschaert (2008), Numerical Solutions for Fractional Reaction-Diffusion Equations, Comp. Math. App.55: 2212–2226.

[31] R. Baeumer, M. Kovacs and M. M. Meerschaert (2007), Fractional reproduction dispersal equations and the heavy tail dispersal kernels, Bulletin of Mathematical Biology. 69:2281-2297.

[32] K. B. Oldham and J. Spanier (1974). The fractional calculus, New York, Academic Press.

[33] R. Metzler and J. Klafter (2000). The random walk's guide to anomalous diffusion: a fractional dynamics approach, Phys. Rep. 339 (1).