African Journal of Mathematics and Computer Science Research Vol. 4(3), pp. 136-158, March 2011
Available online at http://www.academicjournals.org/AJMCSR
ISSN 2006-9731 ©2011 Academic Journals

Full Length Research Paper

Nonlinear analysis of a fractional reaction diffusion model for tumour invasion

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Accepted 20 September, 2010

Mathematical models in general and Reaction Diffusion Models in particular have been rigorously studied and applied in different forms to explain situation in biomedical and allied sciences including the complex tumour microenvironment. They have been proven to be really significant in cancer research. The not so extensively known fractional reaction-diffusion model is presented in this research as a plausible model for the invasion of tumour and its consequences in the human organ in which it resides. In this model we make use of fractional derivatives as a replacement for the normal derivatives to express the diffusion of the tumour cells, normal cells and hydrogen ion concentration. The nonlinear analysis of this model predicts that a death situation always arise if some of the parameters are of a certain magnitude. In this situation, the tumour cells population increases (with an eventual bound after death) by eating up all the normal cells of their host organ. Effectively, the model predicts that the relative interaction between the tumor and normal cells population gives rise to a bifurcation parameter for which a Hopf bifurcation occurs between the period of attack and death. Also the death situation using this model comes faster than the predictions of other models for tumour invasion. This research may therefore give a useful indication of the possible timing of the drugs and dosages required for the treatment or control of tumour progression in human.

Key words: Tumour, fractional reaction diffusion equation, trotter product formula, hopf bifurcation, vasculature, oxygenation, Hypoxia.

INTRODUCTION

In the United States, cancer was second only to heart disease as a cause of death in the late 80s, accounting for 22% of all death. It was also the leading cause of death among women of age between 35 and 74 (Devita et al., 1993). The trend was anticipated to grow in the 90s in which case it was predicted that 100000 new diagnosed cases among 500000 patients in 1992. As at 2006, the mortality rate of cancer was increasingly approaching 100% within 5 years after diagnosis in the United States (Nadja et al., 2006). Factors which have been suggested to directly affect cancer metatases are tobacco, alcohol, occupational hazards, environmental pollution, ionization, solar radiation, medications, virus, diet and nutrition and genetic susceptibility (Kroemer and Reed, 2000; Kroemer et al., 1997). Manifested by a situation of rapid tissue growth, some types of cancers include; prostate, pancreatic, breast, lungs, brain and gastrointestnal cancer. This growth gives rise to nodules which are different from the normal human cells, in their structural characteristics and properties (Robbins et al., 2003; Schwerdt et al., 2005). We call these nodules tumour cells. In this light we defined tumour as an abnormal growth or mass of tissue. A tumour can be either malignant or benign both of which are examples of neoplasia, meaning a process of “new growth” (Devita et al., 1993).

Neoplastic tumours are caused by mutations in DNA of cells, which interfere with a cell's ability to regulate and limit cell division. Accumulation of mutations is needed for a tumour to emerge. For example, mutations that activate oncogenes or repress tumour suppressor genes can eventually lead to tumours (Ramzi et al., 1999). More

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recently, it has emerged that many human cancers, particularly epithelial cancers, are caused by viral infection. The most common causative viruses are members of the Herpesvirus family, which can cause cancers such as kaposi sarcoma and cervical cancer (Devita et al., 1993; Robbins et al., 2003; Ramzi et al., 1999). Also, Tumour can be linked to dysplasia, a term which literally means disordered growth. In a series of figures insitu, Robbins et al. (2003) showed that dyplasia is encountered mainly in epithelia tissues. The original tumour cell undergoes a series of population doubling within a very short time to produce the minimum size which can be clinically detected. The rate of growth of a tumour is determined by the doubling time, the fraction of tumour cells in the replicative pool and the rate at which cells are shed and lost in the growth lesion This uncontrollable multiplication of the tumour cells has been linked to the favourable conditions of the microenvironment on which they reside (Gatenby and Gawlinski, 2003). This environment is made favorable due to cellular vasculation, oxygenation and metabolism (Toma-Dasu et al., 2001; Vaupel et al., 1989; Dewhirst, 1998). The normal cell's microenvironment is different from that of tumour due to the absence of feedback and control mechanisms that regulate the nutrient supply in tumours compared to the normal cells (Raghunand et al., 2003; Toma-Dasu et al., 2002; Vaupel et al., 1989). It has been shown that the fast growing characteristics of tumour determine a poor blood supply that disturbs the delivery of chemical reagent to the affected cells (Alexandru-Dasu et al., 2003). This poor blood supply leads to hypoxia, which helps in increasing the radio resistance of tumour cells. Furthermore, tumour lack a lymphatic system for the drainage of metabolic residues and this helps in increasing the pH of the microenvironment (Gatenby et al., 2006; Toma-Dasu, 2004). An increase in this pH hinders the actions of cytotoxic agents whose actions is favourable only on low pH.

Also, tumour cells evolve resistance to acid–induced toxicity during carcinogenesis, allowing them to survive and proliferates in low pH microenvironments. This permits them to invade and damage adjacent normal cells despites the acid gradient (Gatenby et al., 2006). In another light, when this tumour density has risen above the capacity of the proliferation pool, they diffused outward into neigbouring cells. We refer to the proportion of nodules within the proliferation pool as growth fraction. Therefore, the growth fraction are the same in nature (self-similar) to those pushed outward due to density and quest for nutrient and are connected to them. The normal cells give way for more development of tumour cells as a consequent of this invasion. Toma-Dasu (2004) differentiated parasitisation and angio-genesis based on the biological signals that are sent by the tumour cells to the nearby vessels when they outgrow the diffusion distance of oxygen (Raghunand et al., 2003). This shows that a vast majority of the transformed cells occurs within the proliferation pools. The outward diffusing nodules will establish pools in their microenvironment similar to the original pool. We say the tumour has reached the clinical identity stage at the point where the maximum volume of the proliferation pool has been attain for which any further cell division will lead to diffusion to the immediate surrounding outside the pool (Robbins et al., 2003). Equivalently, this can be referred to as the size for which, the possible first external proliferation is liable to be created and linking the original pool. At this point, spread of tumour cells can be conveniently described by Fick's law (Fedotov and Lomin, 2007).

Many research bodies, structures and individuals have their focus centred on human cancer, its genetics and possible cure. They seek to define the molecular events that control cellular responses to external cures signalling cell division, differentiation or death. Most of these researches have gone a long way to help clarify the molecular mechanisms involved in the development and progression of cancers from tumour cells [Ravi et al., 2000; Graham et al., 1999; Zhang et al., 2000). In this light, molecular genetic techniques are being used to identify novel molecular markers that may prove useful in the early diagnosis or prognosis of cancer and/or be potential therapeutic targets (Cleveland, 2007). The fact that early diagnosis has been very difficult, treatment generally is limited. Proposing a model which can help to explain the disease behaviour before and after the minimum clinically diagnosed size will help in the fight for its eradication. Understanding that most malignant tumours grow in four stages: Malignant changes in target cell, growth of the transformed cells, local invasion and distant metastases is a key issue in the development of the model that can explain this overall behaviour. The smallest clinically detectable size of the tumour comes after the third stage in which case the life cycle of the tumour has been completed (Robbins et al., 2003).

Recently, reaction-diffusion (RD) models have been used to research into cancer, using the model of acid-mediated tumour invasion (Gatenby and Gawlinski, 1996; Gatenby et al., 2006). These models can explain the development of the tumour only after the fraction of cells in the proliferation pools have been attained and the cells start spreading to neighbouring cells. Inside the proliferation pool the diffusion is not normal and does not obey the law of diffusion. The dimension of the cellular volume in this pool compare to the organ is a fraction and therefore cannot be completely explain using ordinary reaction diffusion equations. We proposed fractional reaction diffusion equation for the acid-mediated tumour invasion due based on the following evidence from other research.

TUMOUR AS FRACTAL STRUCTURE

Building on the classic work of Mandelbrot (1983) on

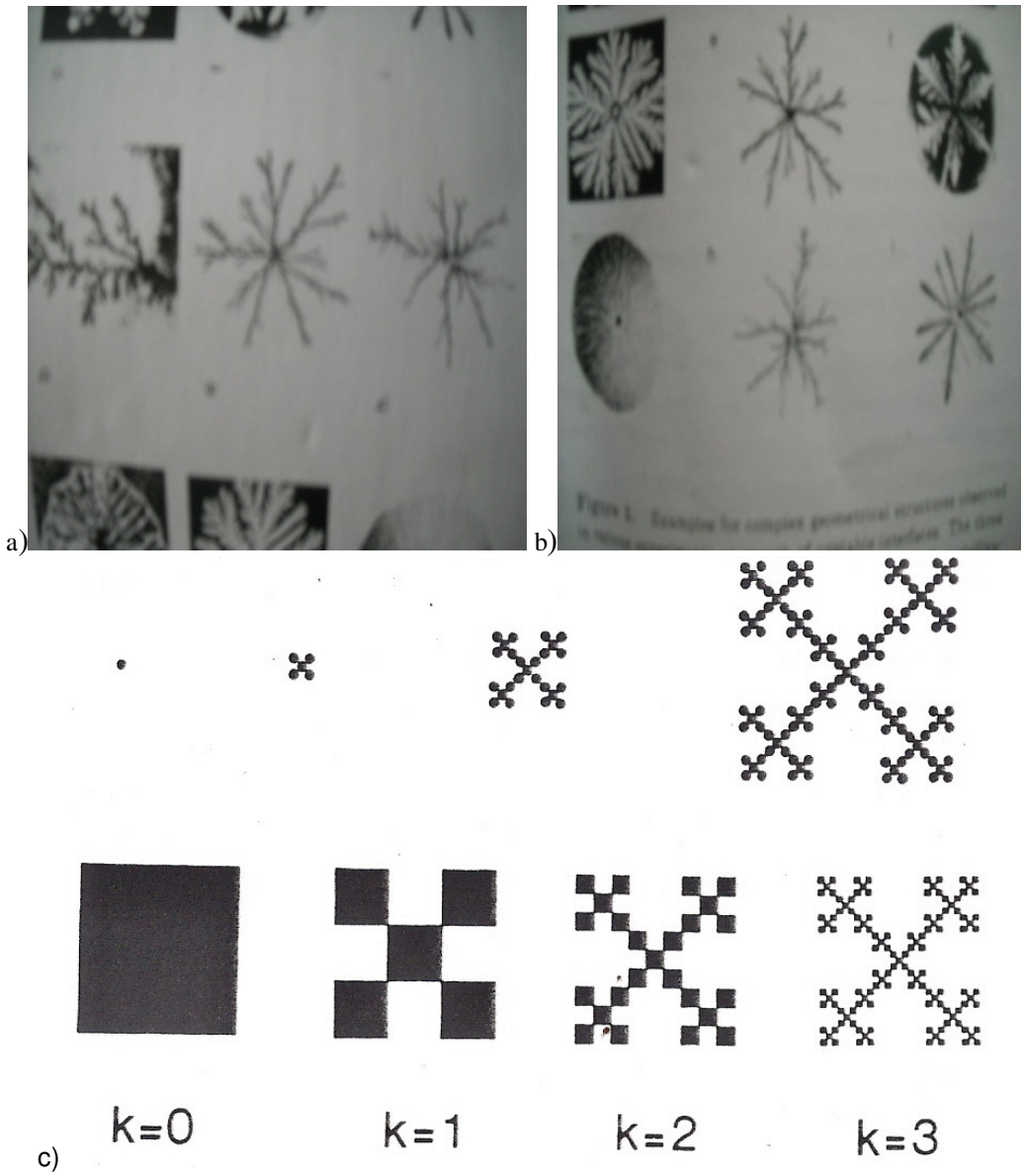

Figure 1. Snap shot (a and b) of the geometrical structure of Fractals; c) a mathematical conception of fractals objects adapted from Temas (1989).

fractals as elucidated by Vicsek (1989), medical scientists have shown that fractal analysis can be used to classify and study complex biological systems. Among these are breast parenchyma (Caldwell et al., 1990), nodular lung diseases (Floyd et al., 1996), tumor angiogenesis (Baish and Jain, 2000) and trabecullar bone (Majumder et al., 1993; Chung et al., 1994; Weinstesh and Majumder, 1994; Fazzalari and Parkinson, 1996). The works of Parkinson and Fazzalari (2000a; b; c; 2001) have shown clearly that tumour have fractal characteristics. The work of Gazit (1996) showed that vascular networks exhibit three types of fractal behaviour and that tumour network displays percolation-like scaling while the normal network belong to diffusion limited scaling (Vicsek,1989) showing clearly that tumours are fractal structures.

From the point of view of Robbins et al. (2003) it can be seen that, the geometrical structure of tumour is similar to the structure of tumour (Falconer, 1990) (Figure 1). This shows that in the development and differentiation of tumour, related cell division takes place and these cells do not stand alone but are linked to the parent cells as branches are linked to a tree. The nucleus of the tumour cells have a ratio of 1:1 to the cell cytoplasm making them different from the normal cells where the nucleus to cytoplasm ratio is 1:6 (Robbins et al., 2003). This means that tumour have a bigger nucleus than normal cells. During growth, tumour nodules moves from the proliferation pool in ever increasing number owing to

shedding, lack of nutrient or apoptosis. We relate this growth phenomena to that of fractals. An object is term a fractal by definition, if measuring its volume, surface or length with a fractional number of d, d-1 etc. dimensional hyper balls, it is not possible to obtain a well converging finite measure for these quantities when changing d over several order of magnitude (Vicsek, 1989). This way, from the starting tumour nodules, the entire volume can be covered by a Ω-ℓ-balls of radius ℓ equal to the radius of the nucleated core and Ω the number of cell doubling multiplied by the number of cells in each doubling operation. As the radius reduces to zero, the number of cells grows to infinity showing that the tumour cells are normal. The nucleus cannot be larger than the cytoplasm so both Ω and ℓ are finite hence the structure of the tumour nodule can be seen as a fractal.
Fractals have the following properties;

1. They are self-similar (scale invariant) structures (Vicsek, 1989; Falconer, 1990; Barkai et al., 2000; Mandelbrot, 1982). This property was also seen in tumur.
2. The volume of fractals which could be completely covered by some number of balls of equal radius is such that as the radius approaches zero, the number of balls increases infinitely. This we also saw in tumour growth above since as the nucleus radius reduces, the tumour cells become normal. Therefore, the number of such small balls to completely cover the entire normal cells certainly is as many as the normal cells hence infinite (Vicsek, 1989; Amann et al., 1988).

Fractional derivatives and fractals

Works of Carpinteri and Mainardi (Carpinteri and Mainardi, 1997; Baeumer et al., 2007; Kolwankar and Gangal, 1996; 1997; 1998), show clearly that fractional derivatives can be used effectively in the analysis of fractal structures. The model involving fractional derivatives in space and time can be understood as a general macroscopic description of an underlying microscopic stochastic process in which particles exhibit both jumps without a characteristic spatial scale and waiting times without a characteristic time scale. This is fractal process.

Fractional diffusion equations are useful where a cloud of particles spread faster than the classical equations predict. In fractional diffusion equations, the second derivative in the spatial variable is replaced by a fractional derivative of order less than two. Fractional reaction diffusion equations therefore have come to solve some of the problems of ordinary reaction diffusion equations. These equations have been used and have proved significant in cases of anomalous diffusion. From recent research, the ordinary reaction diffusion equation is inadequate to model many real situations. Also, solutions to fractional reaction diffusion spread faster than the counterpart of ordinary reaction diffusion equations. For greater details of fractional equations and applications (Podlubny, 2005)

This current work is a fractional reaction counterpart of Gatenby and Gawlinski's reaction diffusion model and the acid mediated model of Gatenby et al. (2006). Their work supported but did not confirm that acid gradient plays an important role in tumour invasion. Taking fractional dimension by treating the tumours as fractals which they are, will lead to better results. Our model is an extension of our earlier work to nonlinear analysis (Oyesanya and Atabong, 2008). As was showed in that work, the model predicts that a bifurcation parameter exists for Hopf bifurcation between the period of attack and death showing that there are critical stages in the development of tumour.Our numerical approximation results in Oyesanya and Atabong (2008) shows that the cancer patient can live with the disease until the bound is exceeded and death follows. We here give a higher nonlinear analysis of our model.

DERIVATION OF THE MODEL

Mandelbrot and Van Ness (1968) 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 (Giona and Roman, 1992; Wyss,1986; Schneider and Wyss, 1989; Jumaire, 1992). A fractional diffusion equation has been proposed for the diffusion on fractals by Giona and Roman (1992) has shown a connection between fractional calculus and fractal structures or fractal processes. These inform our formulation in fractional diffusion equations.

Recent research (Swietach et al., 2007a; b; Sangal et al., 2007; Smallbone et al., 2005) shows that: 1. Increased glycolis of cancer alters the microenvironment by substantially reducing intra-tumoural pH. 2. H+ ions produced by tumour diffuse along concentration gradients into adjacent normal tissues probably carried by a dufering species. 3. Acidification of the extracellular peritumoral environ-ment is advantageous to tumour because it: (a) Induces normal cell death due to necrosis or caspase-mediated activation of p53-dependent apoptosis pathways and death of normal cells produces potential space into which the tumour cells may proliferate. (b) Extracellular acidosis also promotes angiogenesis through acid-induced release of vascular endothelial growth factor and interleukin-8. (c) Acidosis indirectly promotes extracellular matrix degradation by inducing adjacent normal cells (fibroblasts and macrophages) to release proteolytic enzymes such as cathepsin B or increased lycosomal recycling.

(c) Acidosis inhibits immune response to tumour antigens.

In this paper therefore, we have the following considerations for the model:

(1).The tumour cells are parasitic (that is, developed as a result of normal cells destruction).
(2). Acid production increased as a function of the normal and tumour cells. While the tumour cells hasten the production of the acid so as to destroy the normal cells, the normal cells as a result of metabolic activity also accelerate the production of acid.
(3). The normal cells are not comfortable in the acidic medium and this results to their destruction.
(4).The tumour cells are comfortable in the acidic medium and this result to their multiplication at the detriment of the normal cells.
(5).The production and diffusion of the acid is random in time and space respectively in the tumour microenvironment. Due to this anomalous diffusion of the acid produced, the normal and tumour cells will also be subjected to this anomalous diffusion. While the tumour diffused by eating up the normal cells, the normal cells diffused by giving way to the tumour.
(6).The acid produced is also being consumed in the cause of the process.
(7).The diffusivities of the normal and tumour cells depend on each other.
(8).Tumours are fractal structures.
(9).There is connection between fractional calculus and fractal structures.
(10).A fractional diffusion equation has been proposed for the diffusion on fractals.

From the above ten considerations, Let t and x be time and space variables respectively. At any time t, let the population of the normal cells be given by $N_c(x,t)$, that of the tumour cells given by $M_c(x,t)$ and the concentration of hydrogen ion from acid be given by $L_c(x,t)$. The total cell population (concentration) is therefore given by $S_c(x,t)= N_c(x,t) + M_c(x,t)$. S_c is not constant since the cell volume increase as a result of the tumour invasion and rapidlyK_M r espectively. The competitive rate of population survival of the normal cells to the tumour cells is a_M while that of the tumour cells to the normal cells is a_N. The acid provoked death of normal cells is determined by d_N which is a motivating factor for cells leaving the proliferation pool. The per capita rate of multiplication of tumour cells in the proliferation pool is given by $r_M > 0$. Acid production rate as a result of tumour cells out of the proliferation pools is r_{lM}, its re-absorption rate is d_l and its production as a result of normal cell is r_{lN}. The diffusion coefficient of the normal cell as a function of the tumour cells is D_{NM}, diffusion coefficient of tumour cells as a consequence of normal cells is D_{MN}. If D_n, D_m and D_l are representing the constant diffusivities of the normal, tumour and acid, then overall equations for the three populations using fractional derivatives are:

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

$$\frac{\partial M_c}{\partial t} = r_M M_c\left(1-\frac{M_c}{K_M}-a_N\frac{N_c}{K_N}\right)+\frac{\partial^\alpha}{\partial x^\alpha}\left(D_{MN}\frac{\partial M_c}{\partial x}\right) \quad (2)$$

$$\frac{\partial L_c}{\partial t} = r_{lM}M_c - d_c L_c + r_{lN}L_c N_c+\frac{\partial^\alpha}{\partial x^\alpha}\left(D_l\frac{\partial L_c}{\partial x}\right) \quad (3)$$

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

$$D_{MN}=D_m\left(1-\frac{M_c}{K_M}-\frac{N_c}{K_N}\right), D_{NM}=D_n\left(1-\frac{N_c}{K_N}-\frac{M_c}{K_M}\right) \quad (4)$$

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

By, defining new variables, u, v and c as;

$$u=\frac{N_c}{K_N},\quad v=\frac{M_c}{K_M},\quad c=\frac{L_c}{L_0}, \quad (5)$$

and using the following dimensionless quantities:

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

$$\rho=\frac{r_M}{r_N},\quad \xi=\left(\frac{r_N}{D_l}\right)^{1/\beta}x,\quad \beta=1+\alpha,\quad d_2=\frac{D_M}{D_l},\quad d_1=\frac{D_N}{D_l}. \quad (6)$$

we obtain the following non-dimensional equations (Oyesanya and Atabong, 2008)

$$D_\tau^1 u = u(1-u-a_{12}v)-\delta u+d_1\left(-D_\xi^{\beta-1}uD_\xi^1 u-D_\xi^{\beta-1}vD_\xi^1 u+(1-u-v)D_\xi^\beta u\right) \quad (7)$$

$$D_\tau^1 v = \rho v(1-v-a_{21}u)+d_2\left(-D_\xi^{\beta-1}vD_\xi^1 v-D_\xi^{\beta-1}uD_\xi^1 v+(1-u-v)D_\xi^\beta v\right) \quad (8)$$

$$D_\tau^1 c = \delta_1 v(v-c)-\delta_2 cu+D_\xi^\beta c \quad (9)$$

where we have used the notation

$$D_\xi^\beta = \frac{\partial^\beta}{\partial \xi^\beta}, \quad (10)$$

Table 1. Possible equilibrium points.

Code	Normal cells (u)	Tumour 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 tumour cells.ES3 is going to ES6

EXISTENCE AND STABILITY OF EQUILIBRIUM SOLUTIONS

Table 1 shows the equilibrium points obtained from Equations 7 - 9 (Oyesanya and Atabong,2008) .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 tumour cells are surfing in the acidic microenvironment provided $a_{12}a_{21}>1$ (The tumour 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 (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.

FRACTIONAL LINEAR ANALYSIS

We considered a situation where both normal and tumour tissues are well regulated and participate normally in an organ and will therefore not be diffusing in space as a result of each other. This is possible when the tumour cells in an entire organ Under these same assumptions and in addition, the cells are diffusing at a constant rateD_1 for normal cells, D_2 for tumour cells and D_3 for H^+. With these assumptions, all mixed order fractional spatialderivatives are zero and Equations 7 - 9 leads to Equation (11) below. In this equation, if we set $a_{12}=0$, $a_{21}=0$, $\delta_2=0$ corresponding to induced death rate of normal cells by tumour cells, induced death rate of tumour cells by normal cells and re-absorption rate of acid by normal cell respectively zero, the Equation (11) becomes the equations in the model reaction diffusion model suggested (Gatenby and Gawlinski, 1996), provided the diffusion scale $\beta=2$.

$$\begin{aligned} D_\tau^1 u &= u(1-u-a_{12}v)-\delta cu+d_1\left(D_\varsigma^\beta u\right)\\ D_\tau^1 v &= \rho v(1-v-a_{21}u)+d_2\left(D_\varsigma^\beta v\right)\\ D_\tau^1 c &= \delta_1 v(v-c)-\delta_2 cu+D_\varsigma^\beta c \end{aligned} \qquad (11)$$

In Equation (11) we set,

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

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,

$$LU = KU, \qquad (13)$$

(where,

$$L=\begin{pmatrix} D_\tau^1-d_1D_\varsigma^\beta & 0 & 0\\ 0 & D_\tau^1-d_2D_\varsigma^\beta & 0\\ 0 & 0 & D_\tau^1-D_\varsigma^\beta \end{pmatrix},\quad K=\begin{pmatrix} f_u(U^*) & f_v(U^*) & f_c(U^*)\\ g_u(U^*) & g_v(U^*) & g_c(U^*)\\ h_u(U^*) & h_v(U^*) & h_c(U^*) \end{pmatrix}$$

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

Seek for solution of (13) in the form $U=e^{\theta\tau}e^{\sigma i\varsigma}$ and substitute it in Equation (13) we get,

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

We have used the fact that the fractional derivatives of the exponential is generally given by, $D^\beta e^{ax}=a^\beta e^{ax}$. (Oldham and spanier, 1974; Marc, 2004).

Stability of operator Equation (13) 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,

$$\lambda^2-TraceA+DetA,$$

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,

$$3\theta(\sigma) = -\sigma^2(1+d_1+d_2) + (f_u + g_v + h_c) \qquad (14)$$

which is the three components relationship corresponding to what was obtained by many others for the two components ordinary reaction diffusion equation (Chien and Chen, 1998; Mac, 2004). A similar relationship is obtained for the determinant given by,

$$\begin{aligned} DetA = {} & \theta^3 - \theta^2\chi - \theta^2 h_c + \theta d_1 d_2\chi^2 - d_1 d_2\chi^3 - d_1 d_2\chi^2 h_c + \theta d_1\chi g_v - d_1\chi^2 g_v + \\ & - d_1\chi g_v h_c - \theta^2 d_1\chi + \theta d_1\chi^2 + \theta d_1\chi h_c - \theta^2 d_2\chi + \theta d_2\chi^2 + \theta d_2\chi h_c - \theta^2 g_v + \theta\chi g_v + \theta g_v h_c + \\ & - \theta^2 f_u + \theta\chi f_u + \theta f_u h_c + \theta d_2\chi f_u - d_2\chi^2 f_u - d_2\chi f_u h_c + \theta f_u g_v - \chi f_u g_v - f_u g_v h_c - \theta g_c h_v + d_1\chi g_c h_v + \\ & + f_u g_c h_v - \theta f_v g_v + \chi f_v g_v + f_v g_v h_c - f_v g_c h_u - f_c g_u h_v - \theta f_c h_u + d_2\chi f_c h_u + f_c g_v h_u \end{aligned}$$

where, $\chi = (\sigma i)^{\beta}$

if $\beta = 2$ $\chi = -\sigma^2$ and the relation of the determinant becomes (Oyesanya and Atabong, 2008),

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

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. For this value of β, 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 (Murray, 2003). To start with, a situation of Hopf bifurcation phenomenon is possible (Oyesanya, 2005; Chien and Chen, 1998) 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, Trace(A) = 0 and Det(A) > 0.

THE CASE TRACE(A) = 0 AND DET(A) > 0

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

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

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

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

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

Applying the notion of curve sketching as elucidated in calculus, the first derivative,

$\frac{d\theta(\sigma)}{d\sigma}$ of θ with respect to σ is given by,

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

while the second derivative is given by,

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

It is immediate that 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 Euclidian plane. The maximum value occurs at σ =0. A sketch of the contours of $\theta(\sigma)$, for different values of the parameters as can be seen from Figure 2

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 accordingly. 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

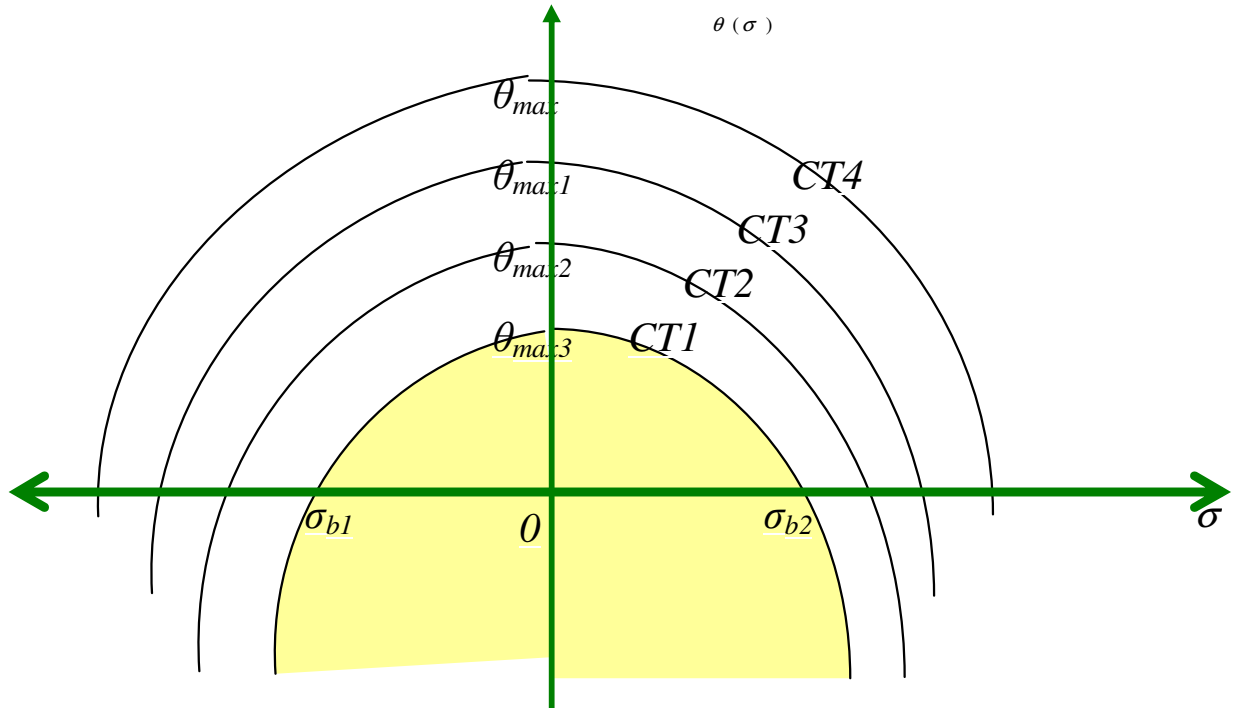

Figure 2. Contours of the spatial variation parameter value of the trace σ against the temporal variation θ

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 deriva-tives 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.

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

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

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, 2008). 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,

$$f_u = 1 - a_{12} - \delta, f_v = 0, f_c = 0, g_u = -a_2\rho, g_v = -\rho, g_c = 0\ h_u = \delta_2, h_v = \delta_1, h_c = -\delta_1 + \delta_2$$

$$\theta_{\max} = \frac{(1 - \delta_1 - a_{12} - \rho - \delta_1 + \delta_2)}{3} = \frac{(1 - 2\delta_1 - a_{12} - \rho + \delta_2)}{3}$$

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 considerations, we see that the steady state ES4 is stable. Therefore, under what condition can the steady states ES3 goes to ES2 or ES4? By substituting ES3 into the above null trace relationship, we get

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

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 Oyesanya and Atabong (2008). 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} is by far greater than a_{21} (denoted as $a_{12}>>>a_{21}>0$) then the Steady state ES4 will be approached from ES3 while if $a_{21}>a_{12}>0$ and $b_1>b_2>0$ are 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 $a_{12}/a_{21}=1$ is a multiple bifurcation point whereby if $a_{12}/a_{21}<1$ we have a sub critical hopf bifurcation of the trivial solution and all other solutions. The case, $a_{12}/a_{21}=1$ we have a supercritical hopf bifurcation of the ES2 solution and subcritical hopf bifurcation of the other solutions. As $a_{12}/a_{21}>1$ 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.

THE CASE $1<\beta<2$, TRACE(A)=0 AND DET(A)>0

In this case,

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

and by substituting,

$$i^\beta=\cos\left(\frac{\beta\pi}{2}\right)+i\sin\left(\frac{\beta\pi}{2}\right),$$

$$TraceA=\left[3\theta-(1+d_1+d_2)(\sigma)^\beta\cos\left(\frac{\beta\pi}{2}\right)-(f_u+g_v+h_c)\right]+i\left[\sigma^\beta\sin\left(\frac{\beta\pi}{2}\right)\right]$$

TraceA=0 if,

$$\left[3\theta-(1+d_1+d_2)(\sigma)^\beta\cos\left(\frac{\beta\pi}{2}\right)-(f_u+g_v+h_c)\right]=0$$

and $\left[\sigma^\beta\sin\left(\frac{\beta\pi}{2}\right)\right]=0$.

However,

$$\left[\sigma^\beta\sin\left(\frac{\beta\pi}{2}\right)\right]=0\Leftrightarrow\sigma=0 \text{ or}$$

$$\beta=2k,\ k\in\{0,1,2,3,...\},.$$

This will contradict the fact that $\beta\in(1,2)$. Hence we cannot get a hopf bifurcation by setting TraceA =0.

THE CASE $1<\beta<2$, TRACE(A)<0 AND DET(A)=0

The expression for the determinant is given by,

$$DetA=\left(\theta-d_1(\sigma i)^\beta-f_u\right)\left[\left(\theta-d_2(\sigma i)^\beta-g_v\right)\left(\theta-(\sigma i)^\beta-h_c\right)-g_ch_v\right]+$$
$$f_v\left[-g_v\left(\theta-(\sigma i)^\beta-h_c\right)-g_ch_u\right]-f_c\left[g_uh_v+h_c\left(\theta-d_2(\sigma i)^\beta-g_v\right)\right]$$

By replacing $i^\beta=\cos\left(\frac{\beta\pi}{2}\right)+i\sin\left(\frac{\beta\pi}{2}\right)$ in the above expression, we get,

$$Det=\left(\left(\theta-d_1\sigma^\beta\cos\left(\frac{\beta\pi}{2}\right)-f_u\right)-id_1\sigma^\beta\sin\left(\frac{\beta\pi}{2}\right)\right)*$$
$$\left[\left(\theta-d_2\sigma^\beta\cos\left(\frac{\beta\pi}{2}\right)-g_v\right)-id_2\sigma^\beta\sin\left(\frac{\beta\pi}{2}\right)*\left(\theta-\sigma^\beta\cos\left(\frac{\beta\pi}{2}\right)-h_c\right)-i\sigma^\beta\sin\left(\frac{\beta\pi}{2}\right)-g_ch_v\right]$$

+

$$f_v\left[-g_v\left(\theta-\sigma^\beta\cos\left(\frac{\beta\pi}{2}\right)-h_c\right)-id_1\sigma^\beta\sin\left(\frac{\beta\pi}{2}\right)-g_ch_u\right]-$$

$$f_c\left[g_uh_v+h_c\left(\theta-d_2\sigma^\beta\cos\left(\frac{\beta\pi}{2}\right)-g_v\right)-id_2\sigma^\beta\sin\left(\frac{\beta\pi}{2}\right)\right]$$

Simplify by collecting real and imaginary parts we get,

$$Det=\left(\theta-d_1\sigma^\beta\cos\left(\frac{\beta\pi}{2}\right)-f_u\right)*$$

$$\left[\left(\theta-d_2\sigma^\beta\cos\left(\frac{\beta\pi}{2}\right)-g_v\right)*\left(\theta-\sigma^\beta\cos\left(\frac{\beta\pi}{2}\right)-h_c\right)-g_ch_v-\sigma^{2\beta}\sin^2\left(\frac{\beta\pi}{2}\right)\right]$$

$$-\left(2\theta-(g_v+h_c)-(d_2+1)\sigma^\beta\cos\left(\frac{\beta\pi}{2}\right)\right)d_1\sigma^{2\beta}\sin^2\left(\frac{\beta\pi}{2}\right)-f_vg_v\left(\theta-h_c-\sigma^\beta\cos\left(\frac{\beta\pi}{2}\right)\right)$$

$$-f_vg_ch_u-f_cg_uh_v--f_ch_c\left(\theta-g_v-d_2\sigma^\beta\cos\left(\frac{\beta\pi}{2}\right)\right)$$

$$-i\left\{\begin{array}{l}d_1\left[\left(\theta-g_v-d_2\sigma^\beta\cos\left(\frac{\beta\pi}{2}\right)\right)\left(\theta-h_c-\sigma^\beta\cos\left(\frac{\beta\pi}{2}\right)\right)-g_ch_v-\sigma^{2\beta}\sin^2\frac{\beta\pi}{2}\right]\\+\left(\theta-f_u-d_1\sigma^\beta\cos\left(\frac{\beta\pi}{2}\right)\right)\left(2\theta-(g_v+h_c)-(d_1+1)\sigma^\beta\cos\left(\frac{\beta\pi}{2}\right)\right)\end{array}\right\}\sigma^\beta\sin\left(\frac{\beta\pi}{2}\right)$$

T

his determinant will be zero if and only if the real and imaginary parts are both zero.

Hence,

Re(Det(A)=0 if

$$Det=\left(\theta-d_1\sigma^\beta\cos\left(\frac{\beta\pi}{2}\right)-f_u\right)*$$

$$\left[\left(\theta-d_2\sigma^\beta\cos\left(\frac{\beta\pi}{2}\right)-g_v\right)*\left(\theta-\sigma^\beta\cos\left(\frac{\beta\pi}{2}\right)-h_c\right)-g_ch_v-\sigma^{2\beta}\sin^2\left(\frac{\beta\pi}{2}\right)\right]$$

-

$$\left(2\theta-(g_v+h_c)-(d_2+1)\sigma^\beta\cos\left(\frac{\beta\pi}{2}\right)\right)d_1\sigma^{2\beta}\sin^2\left(\frac{\beta\pi}{2}\right)-f_vg_v\left(\theta-h_c-\sigma^\beta\cos\left(\frac{\beta\pi}{2}\right)\right)$$

$$-f_vg_ch_u-f_cg_uh_v--f_ch_c\left(\theta-g_v-d_2\sigma^\beta\cos\left(\frac{\beta\pi}{2}\right)\right)=0$$

From where we get that,

Either, $\theta = f_u + d_1\sigma^\beta\cos\left(\frac{\beta\pi}{2}\right)$ or

$$\theta=\frac{1}{2}\left(\begin{array}{l}\left(h_c+\sigma^\beta\cos\left(\frac{\beta\pi}{2}\right)+d_2\sigma^\beta\cos\left(\frac{\beta\pi}{2}\right)+g_v\right)\pm\\\left(\left(h_c+\sigma^\beta\cos\left(\frac{\beta\pi}{2}\right)+d_2\sigma^\beta\cos\left(\frac{\beta\pi}{2}\right)+g_v\right)^2-\right.\\\left.4\left[\left(d_2\sigma^\beta\cos\left(\frac{\beta\pi}{2}\right)+g_v\right)\left(\sigma^\beta\cos\left(\frac{\beta\pi}{2}\right)+h_v\right)-\left(g_ch_v+d_2\sigma^\beta\cos\left(\frac{\beta\pi}{2}\right)\right)\right]\right)^{1/2}\end{array}\right)$$

For simplicity we consider the case where, $\theta = f_u + d_1\sigma^\beta\cos\left(\frac{\beta\pi}{2}\right)$ and state the following condition for hopf bifurcation.

NECESSARY CONDITION FOR HOPF BIFURCATION

Suppose that $\theta = f_u + d_1\sigma^\beta\cos\left(\frac{\beta\pi}{2}\right)$ then it is necessary that the following equalities hold for the system to exhibit a Hopf bifurcation phenomenon.

$$\sigma = \left(\frac{g_vh_c - 2f_u}{(2d_1-(d_2+1))\cos\frac{\beta\pi}{2}}\right)^{1/\beta};$$

$$d_1=\frac{(d_2+1)[f_vg_v+f_ch_c-(f_vg_vh_c+f_ch_cg_v)+f_cg_uh_v+f_vg_ch_u+(f_vg_v+d_2f_ch_c)(g_vh_c-2f_u)]}{g_vh_c(f_vg_v+f_ch_c)+((f_vg_ch_u+f_cg_uh_v)-(f_vg_vh_c+f_ch_cg_v))}$$

$$d_2=\frac{-PO_1\pm\sqrt{PO^2-4*[(g_vh_c-2f_u)+(f_u-g_v)(f_u-h_c)]*PO_2}}{2*[(g_vh_c-2f_u)+(f_u-g_v)(f_u-h_c)]}$$

where,

$$PO_1=\left[\begin{array}{l}(d_1-1)(g_vh_c-2f_u)^2+(g_vh_c-2f_u)(3d_1-1)+(f_u-g_v)(g_vh_c-2f_u)(d_1-1)+\\(f_u-g_v)(f_u-h_c)(2d_1-1)-g_ch_v\end{array}\right]$$

$$PO_2=\left[\begin{array}{l}d_1(d_1-1)(g_vh_c-2f_u)^2+(g_vh_c-2f_u)d_1(2d_1-1)+(f_u-g_v)(g_vh_c-2f_u)(d_1-1)*\\(d_1-1)(2d_1-1)+(f_u-g_v)(f_u-h_c)(2d_1-1)^2-(2d_1-1)g_ch_v-(g_vh_c-2f_u)\end{array}\right]$$

Notice that d_2 has been defined in terms of d_1.

NON LINEAR ANALYSIS

Let $x=\sum_{j=0}^{\infty}\delta_1{}^jx_j,\quad Where\ x=(u,v,c)^T,\ x_j=(u_j,v_j,c_j)^T$ (15)

From Equation 15, we have that,

$$\begin{aligned}D_\tau^1\textstyle\sum_{j=0}^{\infty}\delta_1^ju_j &= \textstyle\sum_{j=0}^{\infty}\delta_1^ju_j(1-\sum_{j=0}^{\infty}\delta_1^ju_j-a_{12}\sum_{j=0}^{\infty}\delta_1^jv_j)-\delta\sum_{j=0}^{\infty}\delta_1^jc_ju+\\&+d_1(-D_\varsigma^{\beta-1}\textstyle\sum_{j=0}^{\infty}\delta_1^ju_jD_\varsigma^1\sum_{j=0}^{\infty}\delta_1^ju_j-D_\varsigma^{\beta-1}\sum_{j=0}^{\infty}\delta_1^jv_jD_\varsigma^1\sum_{j=0}^{\infty}\delta_1^ju_j+\\&+(1-\textstyle\sum_{j=0}^{\infty}\delta_1^ju_j-\sum_{j=0}^{\infty}\delta_1^jv_j)D_\varsigma^\beta\sum_{j=0}^{\infty}\delta_1^ju_j)\\D_\tau^1\textstyle\sum_{j=0}^{\infty}\delta_1^jv_j &= \rho\textstyle\sum_{j=0}^{\infty}\delta_1^jv_j(1-\sum_{j=0}^{\infty}\delta_1^jv_j-a_{21}\sum_{j=0}^{\infty}\delta_1^ju_j)+\\&+d_2(-D_\varsigma^{\beta-1}\textstyle\sum_{j=0}^{\infty}\delta_1^jv_jD_\varsigma^1\sum_{j=0}^{\infty}\delta_1^jv_j-D_\varsigma^{\beta-1}\sum_{j=0}^{\infty}\delta_1^ju_jD_\varsigma^1\sum_{j=0}^{\infty}\delta_1^jv_j\\&+(1-\textstyle\sum_{j=0}^{\infty}\delta_1^ju_j-\sum_{j=0}^{\infty}\delta_1^jv_j)D_\varsigma^\beta\sum_{j=0}^{\infty}\delta_1^jv_j)\\D_\tau^1\textstyle\sum_{j=0}^{\infty}\delta_1^jc_j &= \delta_1(\textstyle\sum_{j=0}^{\infty}\delta_1^jv_j-\sum_{j=0}^{\infty}\delta_1^jc_j)-\delta_2\sum_{j=0}^{\infty}\delta_1^jc_j\sum_{j=0}^{\infty}\delta_1^ju_j+D_\varsigma^\beta\sum_{j=0}^{\infty}\delta_1^jc_j\end{aligned}$$ (16)

Expand to get,

$$
\begin{aligned}
D_\tau^1\sum_{j=0}^{\infty}\delta_1^j u_j &= (\sum_{j=0}^{\infty}\delta_1^j u_j - \sum_{j=0}^{\infty}\delta_1^j u_j\sum_{j=0}^{\infty}\delta_1^j u_j - a_{12}\sum_{j=0}^{\infty}\delta_1^j u_j\sum_{j=0}^{\infty}\delta_1^j v_j) + \\
&\quad -\delta\sum_{j=0}^{\infty}\delta_1^j c_j\sum_{j=0}^{\infty}\delta_1^j u_j + \\
&\quad + d_1(-D_\varsigma^{\beta-1}\sum_{j=0}^{\infty}\delta_1^j u_j D_\varsigma^1\sum_{j=0}^{\infty}\delta_1^j u_j - D_\varsigma^{\beta-1}\sum_{j=0}^{\infty}\delta_1^j v_j D_\varsigma^1\sum_{j=0}^{\infty}\delta_1^j u_j + \\
&\quad + (D_\varsigma^{\beta}\sum_{j=0}^{\infty}\delta_1^j u_j - \sum_{j=0}^{\infty}\delta_1^j u_j D_\varsigma^{\beta}\sum_{j=0}^{\infty}\delta_1^j u_j - \sum_{j=0}^{\infty}\delta_1^j v_j D_\varsigma^{\beta}\sum_{j=0}^{\infty}\delta_1^j u_j))
\end{aligned}
$$

$$
\begin{aligned}
D_\tau^1\sum_{j=0}^{\infty}\delta_1^j v_j &= (\rho\sum_{j=0}^{\infty}\delta_1^j v_j - \rho\sum_{j=0}^{\infty}\delta_1^j v_j\sum_{j=0}^{\infty}\delta_1^j v_j - a_{21}\rho\sum_{j=0}^{\infty}\delta_1^j v_j\sum_{j=0}^{\infty}\delta_1^j u_j) + \\
&\quad + d_2(-D_\varsigma^{\beta-1}\sum_{j=0}^{\infty}\delta_1^j v_j D_\varsigma^1\sum_{j=0}^{\infty}\delta_1^j v_j - D_\varsigma^{\beta-1}\sum_{j=0}^{\infty}\delta_1^j u_j D_\varsigma^1\sum_{j=0}^{\infty}\delta_1^j v_j \\
&\quad + (D_\varsigma^{\beta}\sum_{j=0}^{\infty}\delta_1^j v_j - \sum_{j=0}^{\infty}\delta_1^j u_j D_\varsigma^{\beta}\sum_{j=0}^{\infty}\delta_1^j v_j - \sum_{j=0}^{\infty}\delta_1^j v_j D_\varsigma^{\beta}\sum_{j=0}^{\infty}\delta_1^j v_j)) \\
D_\tau^1\sum_{j=0}^{\infty}\delta_1^j c_j &= \delta_1(\sum_{j=0}^{\infty}\delta_1^j v_j - \sum_{j=0}^{\infty}\delta_1^j c_j) - \delta_2\sum_{j=0}^{\infty}\delta_1^j c_j\sum_{j=0}^{\infty}\delta_1^j u_j + D_\varsigma^{\beta}\sum_{j=0}^{\infty}\delta_1^j c_j
\end{aligned}
\tag{17}
$$

The O(1) solutions for Equation (17) above for the normal, tumour and acid concentration is given (Oyesanya and Atabong, 2008) respectively as follows;

$$u_0(x,t) = \varpi(x)e^{\tau}\,\frac{1}{2\pi}\int_{-\infty}^{\infty} e^{-i\ell\xi}E(-d_1\,|\,\ell\,|^{\beta}\ \tau)d\ell$$

$$v_0(x,t) = \varpi_1(x)e^{\rho\tau}\,\frac{1}{2\pi}\int_{-\infty}^{\infty} e^{-i\ell\xi}E(-d_2\,|\,\ell\,|^{\beta}\ \tau)d\ell \tag{18}$$

$$c_0(x,t) = \left(\frac{\varpi_2(x)}{e^{\delta t}}\int_0^{\infty}\left(\delta_1\varpi_1(x)e^{\rho\tau}\frac{1}{2\pi}\int_{-\infty}^{\infty}e^{-i\ell\tau}E(-d_2\,|\,\ell\,|^{\beta}\ \tau)d\ell\right)e^{\delta\tau}d\tau\right)\left(\frac{1}{2\pi}\int_{-\infty}^{\infty}e^{-i\ell\xi}E(-|\,\ell\,|^{\beta}\ \tau)d\ell\right)$$

where,

$$E\left(-d_1|\ell|^{\beta}\tau\right) = \sum_0^{\infty}\frac{\left(-d_1|\ell|^{\beta}\tau\right)^n}{\Gamma(n+1)} = e^{-d_1|\ell|^{\beta}\tau} \tag{19}$$

is the Mittag-Lefler function (Erdelyi et al., 1955; Del-Castillo-Negrete, 2003).

SECOND ORDER SOLUTIONS {O(2)ANALYSIS}

The second order approximation equation from (17) is given by,

$$
\begin{aligned}
\delta_1\,D_\tau^1 u_1 &= \delta_1 u_1 - \delta_1^{\,2}u_1^{\,2} - \delta_1^{\,2}\delta c_1 u_1 + d_1\delta_1 D_\xi^{\beta}u_1 \\
\delta_1\,D_\tau^1 v_1 &= \rho\delta_1 v_1 - \rho\delta_1^{\,2}v_1^2 + d_2 D_\xi^{\beta}v_1 \\
\delta_1\,D_\tau^1 c_1 &= \delta_1^{\,2}(v_1 - c_1) + \delta_2\delta_1^{\,2}c_1u_1 + D_\xi^{\beta}c_1.
\end{aligned}
\tag{20}
$$

By Cancellation of δ_1 we have,

$$
\begin{aligned}
D_\tau^1 u_1 &= u_1 - \delta_1 u_1^2 - \delta_1\delta c_1 u_1 + d_1 D_\xi^{\beta}u_1 \\
D_\tau^1 v_1 &= \rho v_1 - \rho\delta_1 v_1^2 + d_2 D_\xi^{\beta}v_1 \\
D_\tau^1 c_1 &= \delta_1(v_1 - c_1) + \delta_2\delta_1 c_1 u_1 + D_\xi^{\beta}c_1
\end{aligned}
\tag{21}
$$

The first and the third Equations of (21) are coupled while the second is not so we can easily solve the second and incorporate the result in the first and third to come out with a system of two fractional differential equations.

Now consider the second Equation of 21, we write it as,

$$D_\tau^1 v_1 = \rho v_1 - \rho\delta_1 v_1^2 + d_2 D_\xi^{\beta}v_1 \tag{22}$$

We observe that in the reaction equation, the reactionterm is Lipschitz continuous on any bounded domain. (Appendix 2). We can therefore apply Trotter Product Formula (TPF) (Baeumer et al., 2006) as in the one order approximation to get a solution for *v*.We start by isolating and solving the reaction part of the equation as follows;

$$D_\tau^1 v_1 = \rho v_1 - \rho\delta_1 v_1^2 \tag{23}$$

Solving for v_1, we proceed as follows,

$$
\begin{aligned}
&D_\tau^1 v_1 = \rho v_1 - \rho\delta_1 v_1^2 \\
&\Leftrightarrow\ D_\tau^1 v_1 = \rho v_1(1 - \delta_1 v_1) \\
&\Leftrightarrow\ \log\left|\frac{v_1}{1-\delta_1 v_1}\right| = \rho\tau + k
\end{aligned}
$$

$$\frac{v_1}{1-\delta_1 v_1} = e^{\rho\tau + k} = m(\xi)e^{\rho\tau}$$

$$v_1(\xi,\tau) = \frac{1}{1+\delta_1 m(\xi)e^{\rho\tau}}m(\xi)e^{\rho\tau}.$$

Therefore, the reaction has solution given by,

$$v_1(\xi,\tau) = \frac{1}{1+\delta_1 m(\xi)e^{\rho\tau}}m(\xi)e^{\rho\tau} \tag{24}$$

On the other hand, the diffusion part of the equation is given by,

$$D_\tau^1 v_1 = d_2 D_\xi^{\beta}v_1, \tag{25}$$

and according to the analysis and method shown with first order approximation (Oyesanya and Atabong, 2008) using Riemann-Liouville formula for the fractional Derivative (Podlubny, 2005), the solution of the equation is giving by,

$$v_1(\xi,\tau) = \frac{1}{2\pi}\int_{-\infty}^{\infty}e^{-i\ell\xi}E(-d_2\,|\,\ell\,|^{\beta}\ \tau)d\ell \tag{26}$$

The general solution according to the Trotter –Product – Formula (TPF) can therefore be written as the product of

the Reaction and the Diffusion partial solutions as follows;

$$v_1(\xi,\tau) = \frac{1}{1+\delta_1 m(\xi)e^{\rho\tau}} m(\xi)e^{\rho\tau} \frac{1}{2\pi}\int_{-\infty}^{\infty} e^{-i\ell\xi} E(-d_2 \mid \ell \mid^{\beta} \tau)d\ell;$$

$$ie, v_1(\xi,\tau) = \frac{1}{2\pi}\frac{1}{1+\delta_1 m(\xi)e^{\rho\tau}} m(\xi)e^{\rho\tau}\int_{-\infty}^{\infty} e^{-i\ell\xi} E(-d_2 \mid \ell \mid^{\beta} \tau)d\ell. \quad (27)$$

At this point we substitute the solution for v_1 in (21) and obtain the following coupled systems for u_1 and c_1;

$$\begin{aligned} D_\tau^1 u_1 &= u_1 - \delta_1 u_1^2 - \delta_1 \delta c_1 u_1 + d_1 D_\xi^\beta u_1 \\ D_\tau^1 c_1 &= \delta_1 v_1 - \delta_1 c_1(1-\delta_2 u_1) + D_\xi^\beta c_1 \end{aligned} \quad (28)$$

We write (28) in the form of a system as;

$$D_\tau^1 Y_1 = MD_\xi^\beta Y_1 + WY_1 + F_1, \quad (29)$$

Where,

$$Y_1 = \begin{pmatrix} u_1 \\ v_1 \end{pmatrix}, M = \begin{pmatrix} d_1 & 0 \\ 0 & 1 \end{pmatrix}, W = \begin{pmatrix} 1 & 0 \\ 0 & -\delta_1 \end{pmatrix}, F_1 = \begin{pmatrix} -\delta_1 u_1^2 - \delta_1 \delta c_1 u_1 \\ \delta_1 v_1 - \delta_1 \delta_2 c_1 u_1) \end{pmatrix} \quad (30)$$

CLAIM

The trotter product formula can be applied to the system (29).[Logically we assume the following can be applied for systems in general and prove that the hypothesis for the theorem if stated for a system are satisfied for (29) before stating and proving the full theorem for systems of reaction diffusion equations.]

PROOF

On any suitable Banach space X, MD_ξ^β is a generator of a strongly continuous semi group (Miller and Ross, 1993). Since our space is the space of continuously differentiable functions with the L2-norm, it is a Banach space and therefore suitable to make MD_ξ^β a generator of continuous semi group. In particular, in the set of complex numbers with the L_2-norm, defining H as, $H = WY_1 + F_1(\tau,(Y_1))$, shows that $H: X \to X$ is globally Lipschitz continuous. This is seen from the fact that,

$$\|H(Y_1)\| = \|WY_1\| + \|F(Y_1)\| = \left(\sum_0^\infty |w_i y_i|^2\right)^{1/2} + \left(\sum_0^\infty |f_i(y_i)|^2\right)^{1/2} \le Lc\|Y_1\| \quad (31)$$

since each of the individual functions is Lipschitz continuous. Thus the sum is Lipschitz continuous. Lc is the Lipschitz constant. By making appropriate implications, we see that the function H so defined is Lipschitz continuous. Now since our steady states lies in both X and the domain of the generator (theses are the equilibrium solutions of the fractional reaction diffusion equation) there exist a unique global mild solution for both the reaction and the diffusion parts of the fractional reaction diffusion system. Hence for any initial conditions, the fractional reaction diffusion system has a unit global mild solution.◊

The system for the reaction equations is given by;

$$D_\tau^1 Y_1 = WY_1 + F_1 \quad (32)$$

Since this is a system of ordinary differential equation, we solve it using methods for solving systems of ODEs (Ayres, 1952; Buck and Buck, 1976; Golub, 1996). Solving $Y_1 = e^{W\tau}$. We can write this solution as,

$$Y_1^F = \sum_{i=1}^{2} k_i y_i e^{\lambda_i \tau} \quad (33)$$

where, k_i, λ_i, y_i are the arbitrary constants, the eigenvalues of the matrix W and the eigenvectors corresponding to the eigenvalues respectively.From the matrix W, we immediately see that the eigenvalues are $(1, -\delta_1)$ and the eigenvectors corresponding to these eigenvalues are, (1,0) and (0,1) respectively.The particular solutions are therefore given by,

$$Y_1 * (\tau) = Y_1^F(\tau)\int \frac{1}{Y_1(s)} F_1(Y_1(s))ds \cdot \quad (34)$$

The general solution is given by the sum of the particular solution and the fundamental solution as,

$$Y_1(\tau,x) = Y_1^F(\tau)\int \frac{1}{Y_1(s)} F_1(Y_1(s))ds + \sum_{i=1}^{2} k_i y_i e^{\lambda_i \tau} \quad (35)$$

This solution can be written in terms of the individual cells as,

$$\begin{aligned} u_1(\tau,x) &= k_1(x)e^{\tau}\left(-\delta_1\int e^{-s}(e^s)\left(e^s + \delta e^{-\delta_1 s}\right)ds + 1\right) \\ c_1(\tau,x) &= k_2(x)e^{-\delta_1\tau}\left(\delta_1\int e^{\delta_1 s}\left(v_1(s,x) - \delta_2 e^{-\delta_1 s}e^s\right)ds + 1\right) \end{aligned} \quad (36)$$

On expansion while maintaining the same arbitrary constants we have,

$$u_1(\tau,x) = k_1(x)e^{\tau}\left(-\delta_1\int\left(e^s + \delta e^{-\delta_1 s}\right)ds + 1\right)$$

$$c_1(\tau,x) = k_2(x)e^{-\delta_1\tau}\left(\delta_1\int e^{\delta_1 s}\left(\frac{1}{2\pi}\frac{1}{1+\delta_1} m(\xi)e^{\rho\tau}\int_{-\infty}^{\infty} e^{-i\ell\xi} E(-d_2 \mid \ell \mid^{\beta} \tau)d\ell - \delta_2 e^{-\delta_1 s}e^s\right)ds + 1\right)$$

We simplify this further to get,

$$u_1(\tau,x)=k_1(x)e^{\tau}\left[-k_1(x)\delta_1\left(e^{\tau}-\frac{\delta k_2(x)}{\delta_1}e^{-\delta_1\tau}\right)+1\right]+k_3(x)$$
$$c_1(\tau,x)=k_2(x)e^{-\delta_1\tau}\left(\delta_1\int e^{\delta_1 s}\left(\frac{1}{2\pi}\frac{1}{1+\delta_1}m(\xi)e^{\rho\tau}\int_{-\infty}^{\infty}e^{-i\ell\xi}E(-d_2\,|\,\ell|^{\beta}\,\tau)d\ell\right)ds-\delta_2\delta_1e^{s}+1+k_4(x)\right) \quad (37)$$

The diffusion equation on the other hand will be,

$$D_{\tau}^{1}Y_1 = MD_{\xi}^{\beta}Y_1 \quad (38)$$

whose solution can be written as,

$$Y_1(t,\xi)=\frac{1}{2\pi}\int_{-\infty}^{\infty}e^{-i\ell\xi}E(-M\,|\,\ell\,|^{\beta}\,\tau)d\ell \quad (39)$$

Also, this vector solution can be written out as,

$$u_1(\tau,\xi)=\frac{1}{2\pi}\int_{-\infty}^{\infty}e^{-i\ell\xi}E(-d_1\,|\,\ell\,|^{\beta}\,\tau)d\ell$$
$$c_1(\tau,\xi)=\frac{1}{2\pi}\int_{-\infty}^{\infty}e^{-i\ell\xi}E(-\,|\,\ell\,|^{\beta}\,\tau)d\ell \quad (40)$$

The general solution of the second order approximate solution of the fractional reaction diffusion model can therefore be written as,

$$u_1(\tau,\xi)=\left(\frac{1}{2\pi}\int_{-\infty}^{\infty}e^{-i\ell\xi}E(-d_1\,|\,\ell|^{\beta}\,\tau)d\ell\right)k_1(x)e^{\tau}$$
$$\left[-k_1(x)\delta_1\left(e^{\tau}-\frac{\delta k_2(x)}{\delta_1}e^{-\delta_1\tau}\right)+1\right]+k_3(x) \quad (14)$$

$$c_1(\tau,\xi)=\left(\frac{1}{2\pi}\int_{-\infty}^{\infty}e^{-i\ell\xi}E(-\,|\,\ell|^{\beta}\,\tau)d\ell\right)k_2(x)e^{-\delta_1\tau}$$
$$\left(\delta_1\int e^{\delta_1 s}\left(\frac{1}{2\pi}\frac{1}{1+\delta_1}m(\xi)e^{\rho\tau}\int_{-\infty}^{\infty}e^{-i\ell\xi}E(-d_2\,|\,\ell|^{\beta}\,\tau)d\ell\right)ds-\delta_2\delta_1e^{s}+1+k_4(x)\right)$$

Before we state and prove the TPF for systems, we make the following remark.

REMARK 1

Generally, the fact that the determinant of W is less than 0 indicates that this system of equation has solutions which are stable.

THEOREM 1: (TPF FOR SYSTEMS)

Let $D_{\tau}^{1}Y_1 = MD_{\xi}^{\beta}Y_1 + F(Y_1)$ (42)

be a fractional reaction diffusion equation. Suppose Ψ is a Banach space and $F:\Psi^n\to\Psi^n$ is globally Lipschitz continuous in the Banach space with the appropriate norm. The reaction system of equations has a global solution $Y(t)=S(t)\vec{u}_0$ given by the sum of its fundamental and particular solutions for any initial condition $\vec{u}_0\in\Psi^n$ and the flow generated by F is given by,

$$\vec{u}(t)=S(t)\vec{u}_0=\vec{u}_0+\int_0^t F(\vec{u}(s))ds \quad (43)$$

If MD_{ξ}^{β} is the generator of a strongly continuous semi group $\{T(t)\}_{t\geq 0}$ on Ψ, then the diffusion system has a unique global mild solution $\vec{u}(t)=T(t)\vec{u}_0$ for any initial condition $\vec{u}_0\in\Psi$, and if $\vec{u}_0\in\sum(MD_{\xi}^{\beta})$, the domain of the generator, then this is also the unique global strong solution. Then for any $\vec{u}_0\in\Psi$ the abstract reaction-diffusion system has a unique global mild solution.

$$\vec{u}(t)=\Im(t)\vec{u}_0=T(t)\vec{u}_0+\int_0^t T(t-s)F(\vec{u}(s))ds \quad (44)$$

that can be computed by the Trotter Product Formula,

$$\Im(t)\vec{u}_0=_n\lim_{\to\infty}\left[T\left(\frac{t}{n}\right)S\left(\frac{t}{n}\right)\right]^n\vec{u}_0=_n\lim_{\to\infty}\left[S\left(\frac{t}{n}\right)T\left(\frac{t}{n}\right)\right]^n\vec{u}_0 \quad (45)$$

If $\vec{u}_0\in\sum(MD_{\xi}^{\beta})$ and $F:\Psi^n\to\Psi^n$ is continuously differentiable, then 44 is the unique global strong solution of the abstract reaction diffusion equation and this strong solution can also be computed via the TPF.

PROOF. (The case for a single equation was proved in Baeumer et al., 2006)

Suppose $F:\Psi^n\to\Psi^n$ is globally Lipschitz continuous, then it is known that for all vector $\vec{u}_0\in\Psi$ there exist a unique global mild solution $\vec{u}(t):=\Im(t)\vec{u}_0$ of (44) such that,

$$\left\|\Im(t)\vec{u}_0-\Im(t)\vec{v}_0\right\|\leq G_T\left\|\vec{u}_0-\vec{v}_0\right\|,\quad t\in[0,T] \quad (46)$$

Since the reaction system is a special case of the reaction diffusion system, with the generating operator $MD_{\xi}^{\beta} = \vec{0}$, it follows that the reaction system has a unique mild solution given by,

$$\vec{u}(t) = T(t)\vec{u}_0 + \int_0^t T(t-s)F(\vec{u}(s))ds \quad (47)$$

with $T(t)\vec{u}_0 = \vec{u}_0$, and hence,

$\vec{u}(t) = S(t)\vec{u}_0 = \vec{u}_0 + \int_0^t F(\vec{u}(s))ds$ holds for all t>0.This is also a strong solution, since if $\vec{u}$ and F are continuous, then $t \mapsto F(\vec{u}(t))$ is continuous (componentwise continuity) and $t \mapsto \int_0^t F(\vec{u}(s))ds$ is differentiable (component wise differentiability) with, $\left(\int_0^t F(\vec{u}(s))ds\right)' = F(\vec{u}(t))$ (by differentiation of the vector function). Hence, $t \to \vec{u}(t)$ is also differentiable as sum of differentiable functions. Therefore, $\vec{u}$ is a strong solution and the solution, $\vec{u}(t) = T(t)\vec{u}_0$ is a unique global strong solution of the reaction system since the diffusion system is also a special case of the reaction diffusion system.

Furthermore, since the initial values are taken at the steady state, $u_0 \in \Sigma\left(MD_{\tau}^{1}\right)$, *u* is a global strong solution (the single value proof is shown in (Arendt et al., 2001). The system solution operator, $\Im(t)u_0$ to the abstract reaction diffusion system can therefore be computed by the Trotter product Formula,

$$\Im(t)\vec{u}_0 = \lim_{n\to\infty}\left[T\left(\frac{t}{n}\right)S\left(\frac{t}{n}\right)\right]^n\vec{u}_0 = \lim_{n\to\infty}\left[S\left(\frac{t}{n}\right)T\left(\frac{t}{n}\right)\right]^n\vec{u}_0, \quad \vec{u}_0 \in \Psi \quad (48)$$

(Brezis and Pazy, 1972; Cliff et al., 2004; Miyadera and Oharu, 1970). If $u_0 \in \Sigma\left(MD_{\tau}^{1}\right)$ and $F : \Psi^n \to \Psi^n$ is continuously differentiable, then u is also a strong solution (Pazy, 1983).

NUMERICAL APPROXIMATION OF SOLUTIONS

In order to study the behaviour of these solutions, we use numerical methods. The Gauss-Hermite formula was used to carry out the integration. The integrands were all approximated using the Hermite Interpolation polynomials (Alfio and Alberto, 1997; Carl-Erik, 1985). As a quick reminder for easy reading, given a function f(x) as the integrand, the Gauss-Hermite formula is given in Alfio and Alberto, (1997).

$$\int_{-\infty}^{\infty} f(x)dx = \int_{-\infty}^{\infty} e^{-x^2}[e^{x^2}f(x)]dx = \sum w(x_k)[e^{x^2}f(x_k)] + R_n(x)$$

where, x_k is the k^{th} zero of the Hermite polynomials $H_n(x)$ also defined as follows;

$$H_n(x) = (-1)^n \exp(x^2)\frac{d^n}{dx^n}\exp(-x^2).$$

$$w(x_k) = \frac{2^{n-1}n!\sqrt{\pi}}{n^2[H_{n-1}(x_k)]^2}, \; R_n(x) = \frac{n!\sqrt{\pi}}{2^n(2n)!}f^{(2n)}(x).$$

With a program designed in visual basic, we obtain the approximate solutions presented in the appendices.

DISCUSSIONS

Our analytic solution of the *O(2)* system can therefore be written as;

$$v_1(\tau,\xi) = \frac{1}{2\pi}\frac{1}{1+\delta_1}m(\xi)e^{\upsilon\tau}\int_{-\infty}^{\infty}e^{-i\ell\xi}E(-d_2 \mid \ell \mid^{\beta}\tau)d\ell.$$

$$u_1(\tau,\xi) = \left(\frac{1}{2\pi}\int_{-\infty}^{\infty}e^{-i\ell\xi}E(-d_1 \mid \ell \mid^{\beta}\tau)d\ell\right)k_1(\xi)e^{\tau}\left[-k_1(\xi)\delta_1\left(e^{\tau} - \frac{\delta k_2(\xi)}{\delta_1}e^{-\delta_1\tau}\right)+1\right]+k_3(\xi) \quad (49)$$

$$c_1(\tau,\xi) = \left(\frac{1}{2\pi}\int_{-\infty}^{\infty}e^{i\ell\xi}E(-\ell^{\beta}\tau)d\ell\right)k_2(\xi)e^{-\delta_1\tau}\left(\delta_1\int e^{\delta_1\tau}\left(\frac{1}{2\pi}\frac{1}{1+\delta_1}m(\xi)e^{\upsilon\tau}\int_{-\infty}^{\infty}e^{i\ell\xi}E(-d_2\mid\ell\mid^{\beta}\tau)d\ell\right)ds + \delta_2\right)+1+k_4(\xi)$$

If our initial conditions are taken at the steady states, then the steady state $(u_0^*, v_0^*, c_0^*) = (0,0,0)$, is un realistic because in this case, the analytic solution all goes to zero. Therefore any perturbation starting from this state dies down leading to stability. Even though, the state can be seen (some how) as stable from the point of view of small perturbations, it cannot be realistic to have such a state. At least the normal cells existed before the disease attack came resulting in the proliferation of tumour cells. On the other hand, the steady state, $(u_0^*, v_0^*, c_0^*) = (0,1,1)$ shows that starting with these values as the initial condition, and substituting them in place of the functions, $(m(\xi), k_2(\xi), k_1(\xi))$, we see that the normal cells dies in time, while the tumour cells increase with an eventual bound coming from the function,

$$\int_{-\infty}^{\infty}e^{-i\ell\xi}E(-d_2 \mid \ell \mid^{\beta}\tau)d\ell \quad (50)$$

This therefore, gives the decay rate of host the normal cell, after the disease has manifested and kills their host. In a similar manner, the acid concentration increases, but also decays with time. The rate of decay is faster for the acid than for the tumour.This is realistic because the acid is seen as the medium for which tumour cells grow. So if it does not stop then the propagation of the tumour cells will not be discontinued. This is easily seen from the fact that the factor, $\frac{1}{e^{\delta_1 t}}$ multiply the entire expression representing the acid concentration.

The third steady state, $(u_0{*}, v_0{*}, c_0{*}) = (k{*}, 1-k{*}, b_1 - b_2 k{*})$ is the cohabiting steady state. Replacing the initial condition with these values shows that, all the three interacting species are cohabiting. Setting the value of 1 for k* shows that the disease will be under control since v_0 goes to zero. But the TDM suggest that this situation is impossible hence we shall assume that k* is not 1. We can also see that as k* approaches 1, the normal cells as well as the concentration of acid in the tumour region gradually increases. In this case, a patient with a tumour, will keep living with the growth as long as the acid production in the proliferation pool is not exceeded (.Since we are considering that the model is a dead model, it means a thorough study (possibly higher order analysis) of this model will give a better explanation and possible treatment for cancer. It is also realistic to consider a typical homogenous Neumann boundary conditions for all the interacting species in the model since in most situation, we have tumour affecting only particular organ in their host such as pancreas, lungs, prostrate, breast etc. and do not generally exceed these organs into another neighbouring organ.The fourth steady state is therefore stable just in case k* above is 1. In this case, the disease is under control but it is not realistic as has been shown. Using the fifth steady state for our initial conditions, we see that this steady state is unstable and moves to the third case in the long run. The sixth steady state is a consequence of the third as a result of prolongs time. It is therefore, the dead stage of all the normal cells after the attack.

The numerical approximation confirms the trend of the solutions discussed above, with all the solutions eventually turning to zero. As seen in the approximate solutions, a comparison of the tumour population and normal cell population after the diagnosis of the disease shows that the tumour can be contained just in case it is diagnosed early enough (simulations 4 and 5 in Appendix1). The value of the integrals using even numbers of interpolation polynomials have amplitude higher than those of odd number.This is due to the presence of only even powers terms in these polynomials.Since the solutions are auxiliary due to complex terms, we have presented the real solution, separate from the imaginary solution. From the plots, it can be seen that the solutions are out of phase with a phase difference of π. These solutions also portray that, there is quick convergence for small values of x and constant t than for large values of x (See Simulations 1 and 2 and 3 in Appendix 1) for the real and imaginary solutions respectively. For higher fractions, the oscillations are faster with higher amplitude than for lower fractions. For our approximations, we consider 1.7 and 1.8, the value for t was 10, ρ was taken as 1.5.

CONCLUSION

The first order and second order approximate solutions of a fractional reaction diffusion model for tumour invasion has been analysed. From the analysis, we see that this model is illuminating. Our analysis shows that an early diagnosis lends to containment of the disease. We also have quick convergence for small values of x and constant t than for large values of x. In addition, our analysis also shows that for higher fractions, the oscillations are faster with high amplitude than for lower fractions; showing that once the initial ratio of tumour to normal cells in the proliferation pool increased, the faster the attainment of MCD size and the faster the growth rate. A sense of this will easily identify the extent to which the tumour has gone even if its secondary and tertiary pools have not fully established themselves in the region. Higher order approximation we believe will give more interesting phenomenon. Also the consideration of different boundary conditions for this model will beyond reasonable doubt produce some interesting scientific results. These situations and more will be subject for consideration in our subsequent research.

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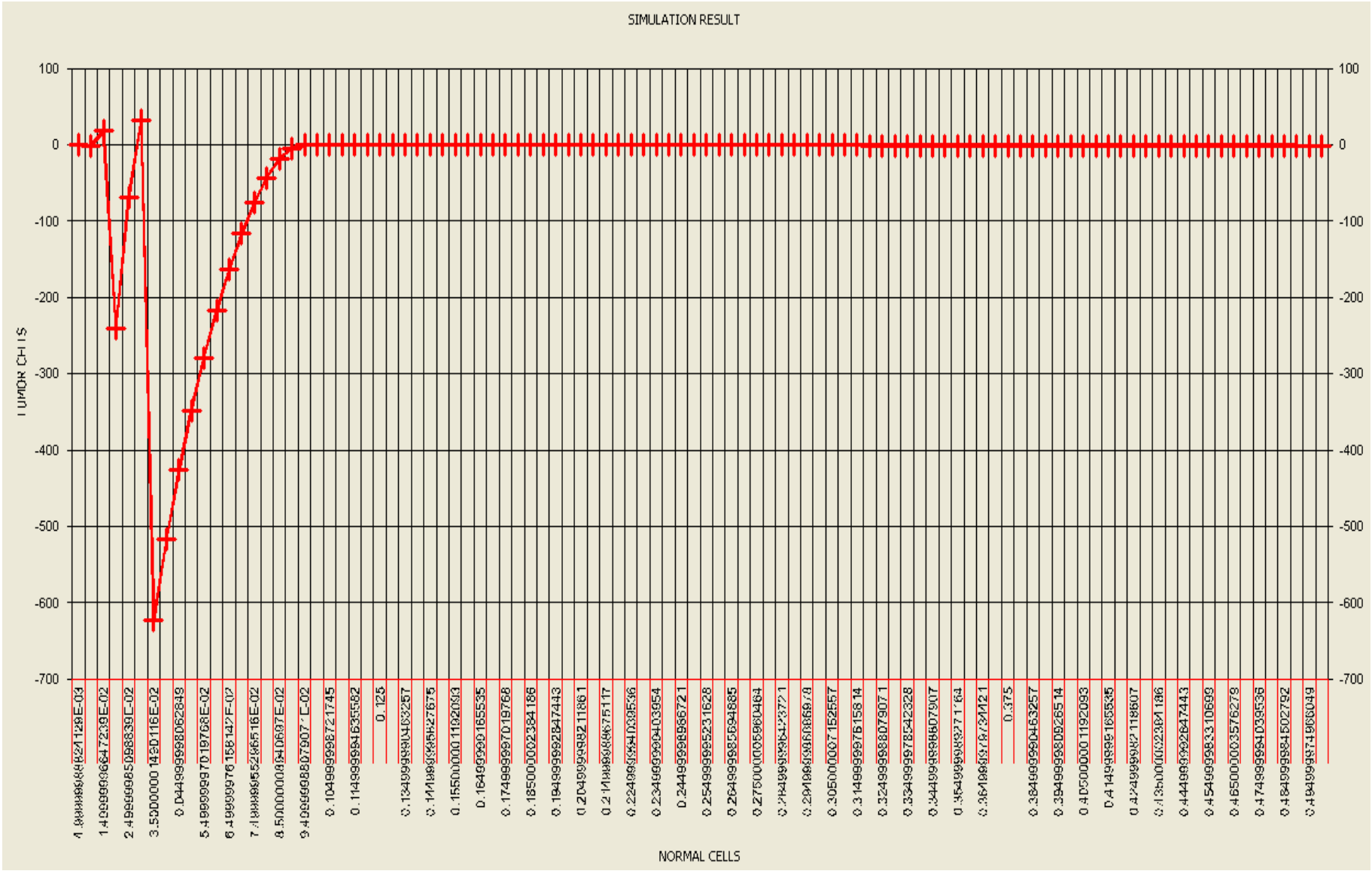
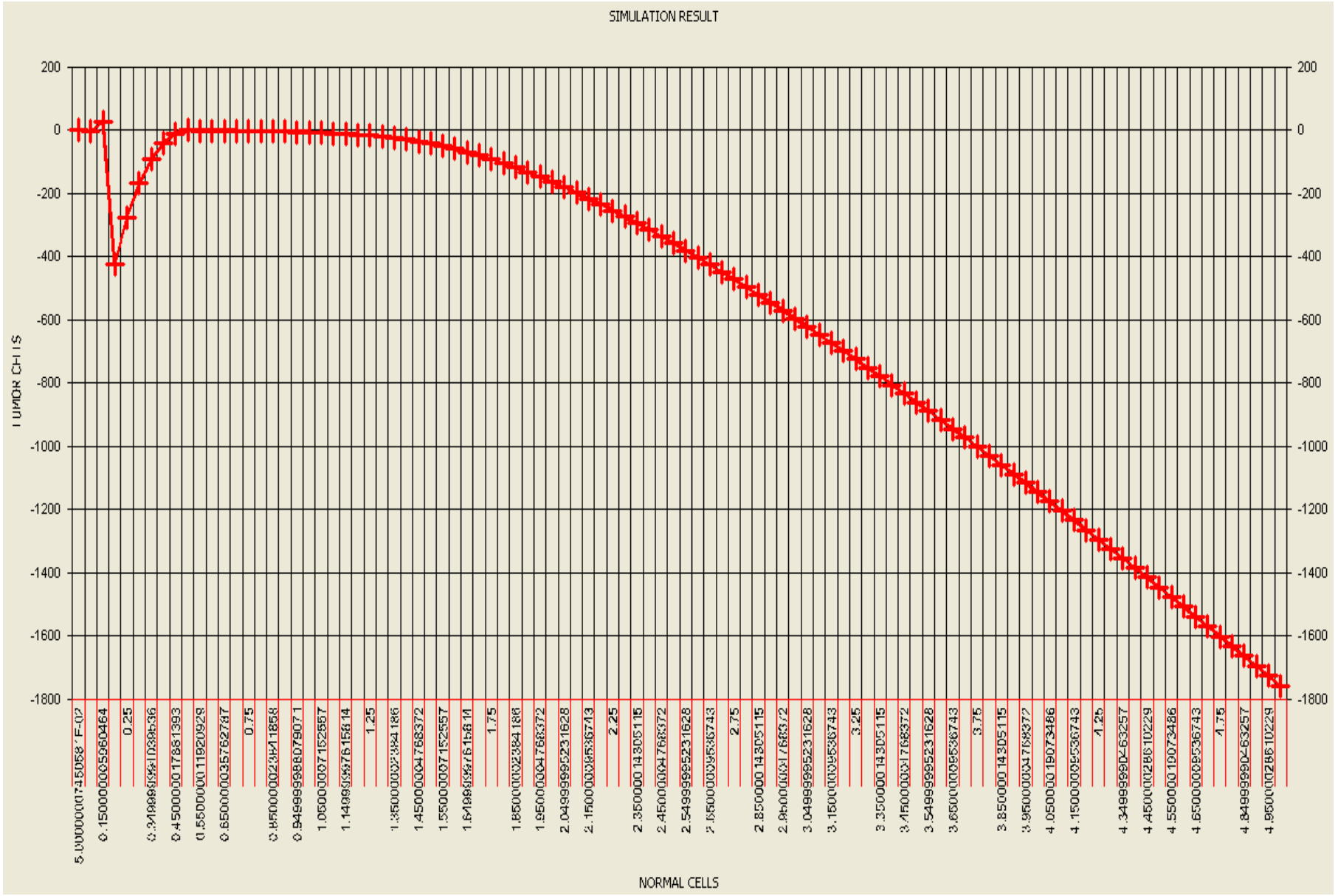
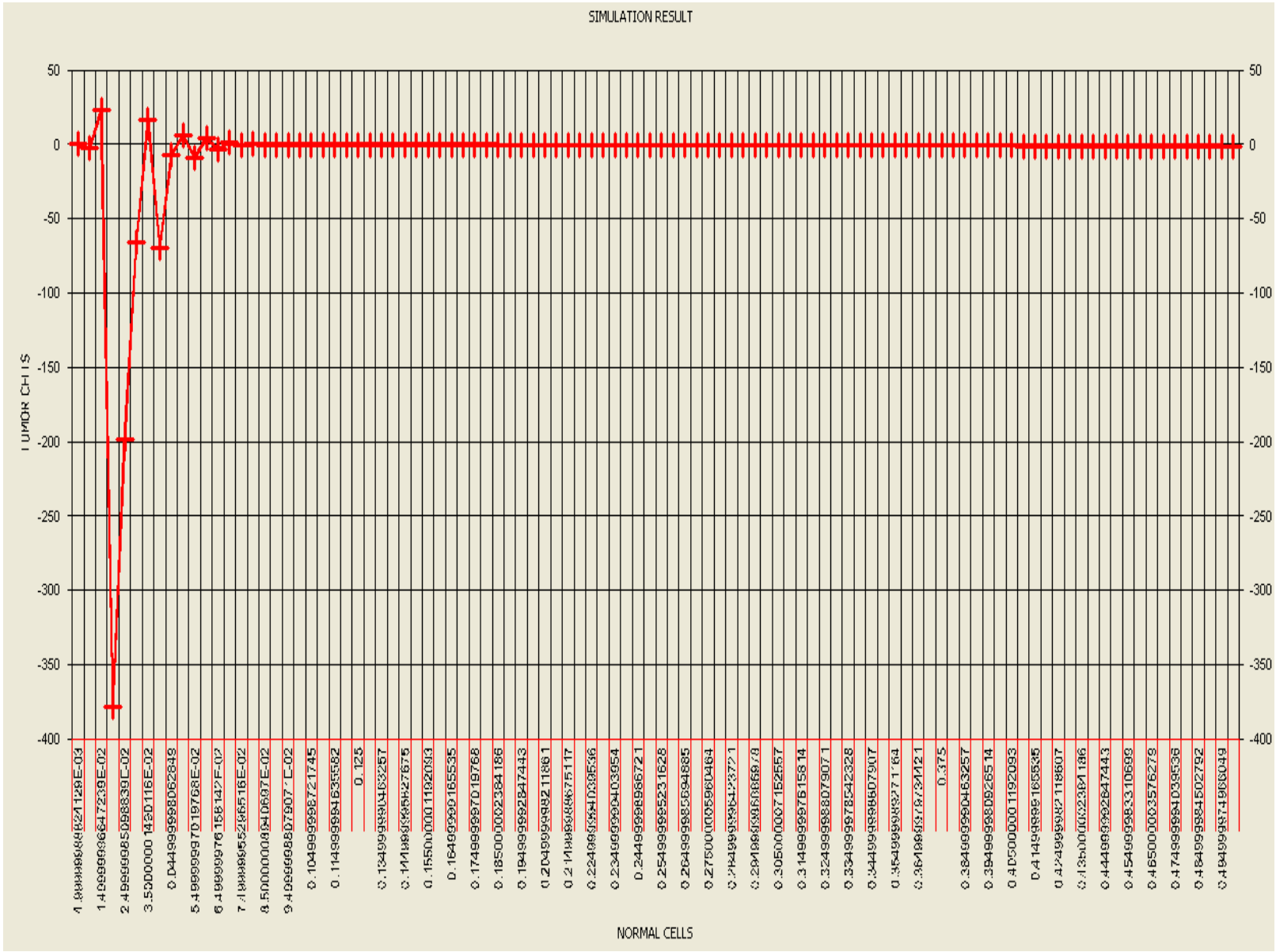
APPENDIX 1.



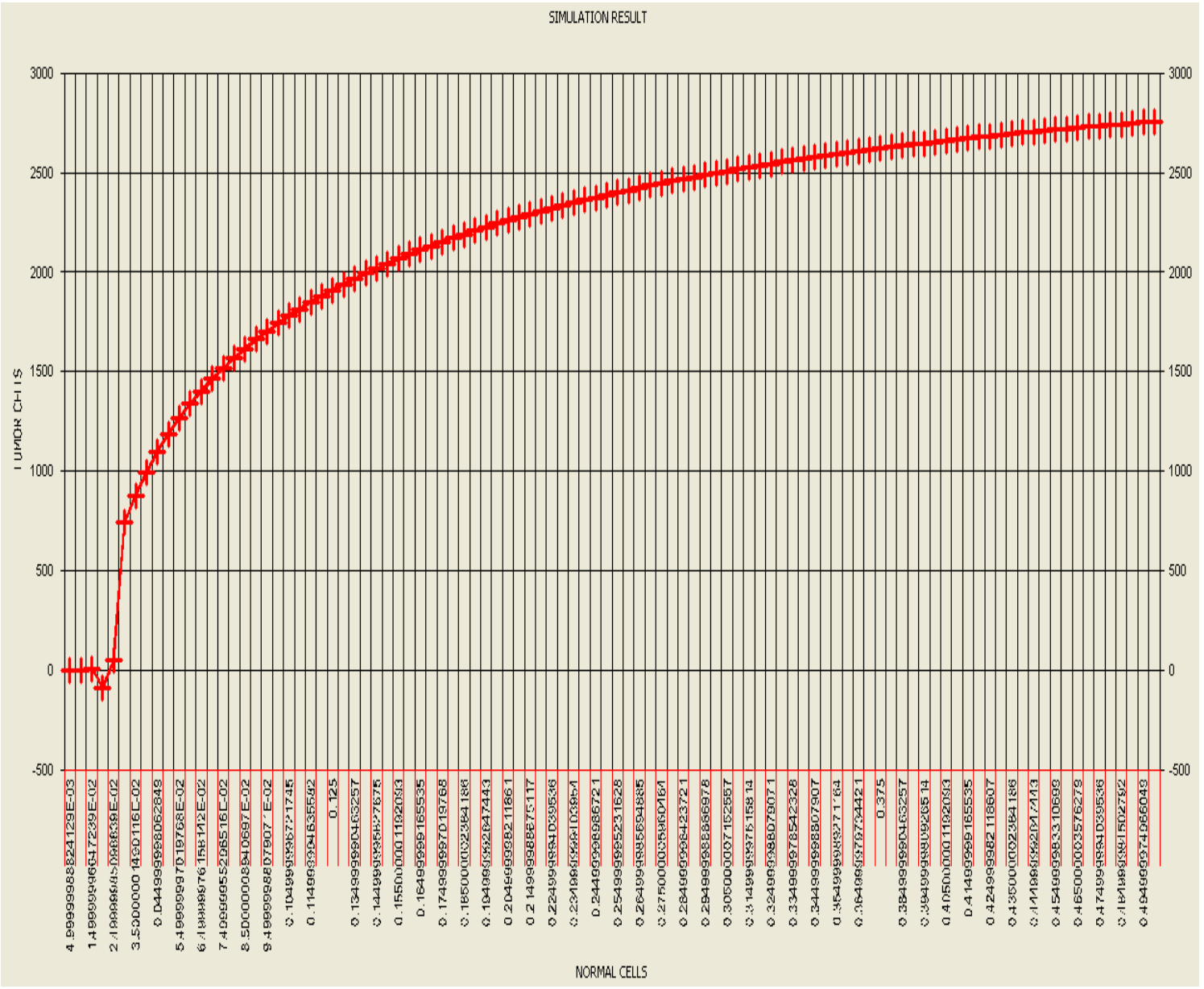
Simulation 1. A plot of the tumour cells against normal cells, Number of sample points 100, step size=0.005, Initial value 0.1.



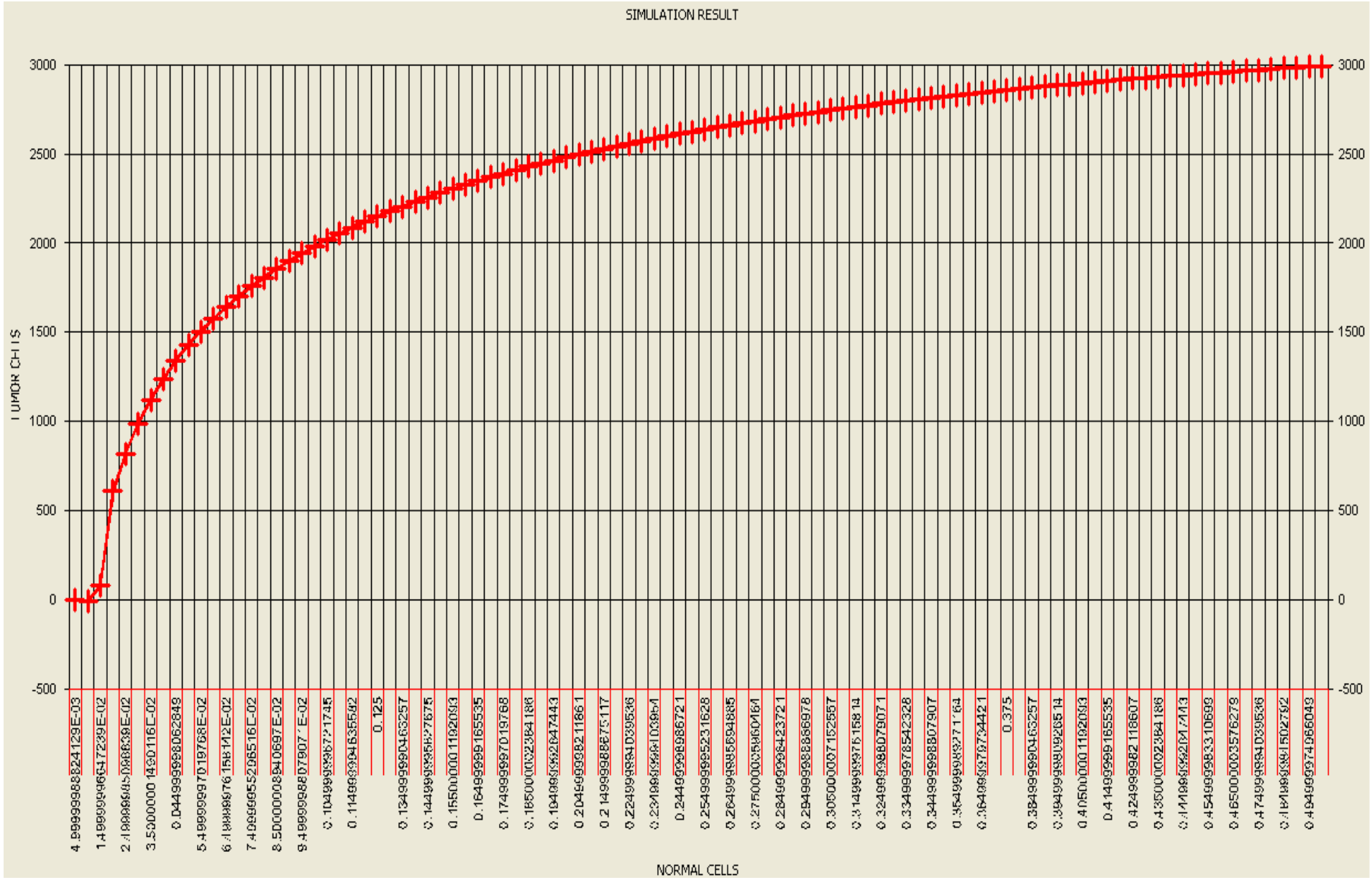
Simulation 2. A plot of the tumor cells against normal cells. Number of sample points 100, step size=0.05, Initial value 0.1.



Simulation 3. A plot of the tumour cells against normal cells. Number of sample points 100, step size=0.005, initial value 0.125.



Simulation 4. A plot of the tumour cells against normal cells. Number of sample points 100, step size=0.005, Initial value 0.05.



Simulation 5. A plot of the tumor cells against normal cells. Number of sample points 100, step size=0.005, Initial value 0.5.

APPENDIX 2

Proof of Lipschitz continuity of Equation (22)

Consider,

$$D_{\tau}^{1} v_1 = \rho v_1 - \rho \delta_1 v_1^2,$$

where the reaction term is, $\rho v_1 - \rho \delta_1 v_1^2$.

Let, $f(v_1) = \rho v_1 - \rho \delta_1 v_1^2$

Then,

$$\|f(y) - f(z)\| = \left\|\rho y - \rho \delta_1 y^2 - \rho z + \rho \delta_1 z^2\right\|$$
$$|\rho| \left\| y - \delta_1 y^2 - z + \delta_1 z^2 \right\| = |\rho| \left\| (y - z) + \delta_1 (y^2 - z^2) \right\|$$
$$\leq |\rho| \left(\|(y - z)\| + \left\| \delta_1 (y^2 - z^2) \right\| \right) = |\rho| \left(\|(y - z)\| + \left\| \delta_1 (y - z)(y + z) \right\| \right)$$
$$\leq |\rho| \left(\|(y - z)\| \left(1 + \left\| \delta_1 (y + z) \right\| \right) \right) = |\rho| \left(1 + \left\| \delta_1 (y + z) \right\| \right) \left(\|(y - z)\| \right)$$
$$= M \left(\|(y - z)\| \right),$$
$$Where, M = |\rho| \left(1 + \left\| \delta_1 (y + z) \right\| \right).$$

In any bounded domain, M is bounded hence f is Lipschitz continuous.