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Graphical analysis of damage mechanics model of cancer

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Abstract

This study exposed the action of oxidative stress on the matrix wall that had tumor (voids), that led to cancer and it illustrated the initiation, growth and coalescence of cancer. The analytic solution showed that the magnitude of stress that led the tumor to rupture was $250kN$ and the time taken to rupture was 100days. The solution showed that the environmental factor that affected the tumor that led to rupture (cancer) was temperature given as θ between $85^0 - 100^0$ c. The model result also showcased that the amplitude of the stress in the tumor that led to coalescence was $2000kN$ and the time taken to coalescence was 100days. Finally, the solution to the model ascertained that it took between 80 -100days for the stress to act on a tumor tissue before it ruptures. Graphs were plotted to illustrate the following actions: rate of growth of cancer cells against the rate of destruction of cells by the cancer cell, the amount of stress applied on tumor against the time taken for tumor to rupture, the amount of stress that will lead solid tumor to coalescence to form cancer. Finally, the analytic solution of the study demonstrates that cancer cells exist right in the solid tumor as a result of oxidative stress losing its bonding power. The system showed significant effect and was found to be stable with growing cancer cells. The study elucidated that the model equations were found physically existing in a disease called "Acha – Ero or (N'shi Calabar)" andMATlab R2015a was used in plotting the graphs.

Keywords: Damage, Oxidative Stress, Traction Force, Solid –Tumor, Acha –Ero and Cancer.

1 Introduction

It is globally seen that stress and cancer is everywhere in the world. Every organism is passing through stress whether induced or natural stress and cancer in living organisms. Thus, the mechanics of damage is the study through mechanical variables of the mechanisms involved in the deterioration of materials or tissueswhen subjected to loading [26]. Damage mechanics is concerned with the representation or modeling of damage of materials or tissues that are suitable for making

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engineering extrapolationsor predictions about the initiation, propagation and fracture of materials without resorting to a microscopic description that would be too complex for practical engineering analysis [23]. Damage mechanics illustrates the typical engineering approach to model complex phenomena. Damage mechanics shows the idea of propagation, initiation and coalescence of voids (tumor) through the tumor microenvironment under the influence of oxidative stress in promoting cancer. The statement of problem is to determine how solid tumors of soft tissue cell form voids, caused the initiation, coalescence and growth of cancer cells under the influence of oxidative stress.Thus, Cancer is not only one disease. Cancer can start from any place in the body. It starts when cells grow out of control and crowd out normal cells. This makes it difficult for the body to function the way it should. Cancer can be treated very well for many people. In fact, more people than ever before lead full lives after cancer treatment. There are different types of cancer. Cancer can start in the lungs, the breast, the colon, or even in the blood. Cancers are alike in some ways but different in the way they grow and spread [3]. Cancer also propagates, grows, coalescence and ruptures in the body of some organisms.

1.1 Cancer Propagation and Movement

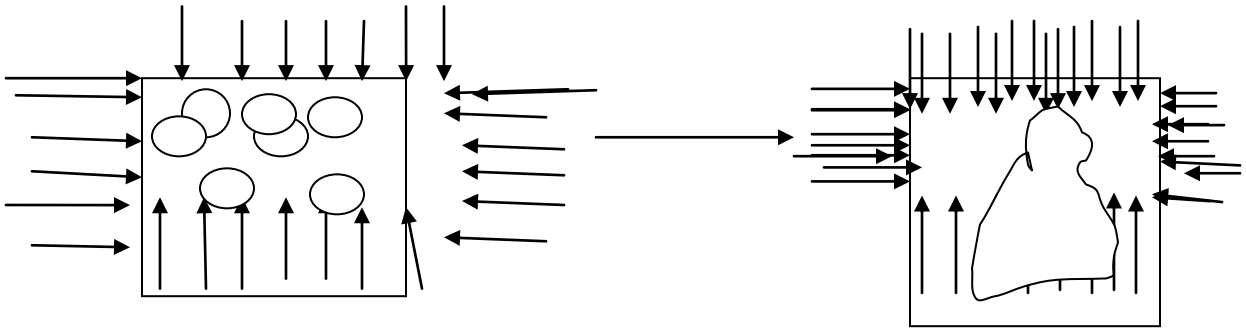
Cancer can move as a fluid and also as a solid. This characteristic makes it a viscoelastic material or tissue or cell or body. Solid cancers are defined as abnormal cellular growths in "solid" organs such as the breast or prostate, as opposed to leukemia, a cancer affecting the blood, which is liquid. Solid tumors may be benign (not cancer), or malignant (cancer). Solid cancer or solid tumor Oncology is a malignancy that forms a discrete tumor mass eg, cancer of brain, breast, prostate, colon rectum, kidney; sarcoma; melanoma, in contrast to lympho proliferative malignancies e.g, leukemia, which may diffusely infiltrate a tissue without forming a mass. Tumors can develop in many parts of the body including the brain, kidneys, liver and bones. These sick cells crowd out healthy cells and keep them from functioning. Common types of solid tumor (cancers) include neuroblastoma, Ewing sarcoma and Wilms tumors.

1.2 Oxidative Stress

Stress is felt at some point in live when an individual feels so busy with work without having a rest. Stress induces signals that can cause cells to develop into tumors. It can be persistent, which means it is long lasting and often gets worse over time. In small doses, stress can be positive, making us more alert and improving our performance. But long periods of stress can contribute to high blood pressure and mental health problems such as anxiety and depression. However, stressful and strenuous events (overuse) performed at one particular part of the body can alter the levels of hormones in the body and affect the immune system. In which case, these changes could lead to cancer.

Oxidation is the transfer of electrons from one atom to another and represents an essential part of aerobic life and normal metabolism, since oxygen is the ultimate electron acceptor in the electron flow system that produces energy in the form of ATP [10]. However, problems may arise when the electron flow becomes uncoupled (transfer of unpaired single electrons), generating free radicals: the oxygen-centered free radicals are known as reactive oxygen species (ROS). In addition to the ROS radicals, in living organisms, there are also other ROS non-radicals. It is accepted that ROS play different roles *in vivo*. Some are positive and are related to their involvement in energy production, phagocytosis, and regulation of cell growth and intercellular signaling, and synthesis of biologically important compounds [19].

Hence, oxidative stress results from an imbalance between unstable reactive species lacking one or more unpaired electrons (superoxide anion, hydrogen peroxide, hydroxyl radical, reactive nitrogen specie) and antioxidants. Oxidative stress can be generated by ultra-violet light exposure, ionizing radiation or carcinogen exposure. Beneath oxidative stress, activated stromal cells generate tumor enhancing signals. Under oxidative stress, the tumor stromal releases high energy nutrients that fuel cancer cells and facilitate their growth and survival. Among the many factors influencing development, progression and metastasis, oxidative stress is important in the initiation and preservation of cancer progression.



Case a tumor state Case b cancer state

Figure 1: Illustration of oxidative stress acting on the matrix wall containing tumor (voids) which coalescence and lead to cancer.

Thus, the figure above shows the actions of the oxidative stress on the matrix wall that causes mutations of the affected cells and leads to cancer.Considerable data exists to support the premise that a lack of antioxidant enzymes tips the balance toward cancer initiation [35]. Mechanical properties such as the stress and strain in the tissue can modulate the growth of cancer [35]. Residual stress has been shown to exist in arteries. The cutting experiments in soft tissue revealed the presence of residual stresses and a stress-free state may not be obtainable.

Stress →Mutations → Cancer: Mutation is a damage carried out in the body. Stress causes mutation and mutation causes cancer to the tissues and cells in the body. Stress is a normal response to feeling threatened or to face challenge when the organism is not sure of meeting. It can be chronic, which means it is long lasting and often gets worse over time. Tumor growth can most likely be sustained either by rare cancer stem-like cells or by selected aggressive clones or both, and the nature of the mutations, the cell of origin, and its environment can also contribute to tumor-cancer propagation [42].

Mutation is a permanent alteration of the nucleotide sequence of the genome of an organism, virus, or extra chromosomal DNA or other genetic elements. Mutations result from damage to DNA which is not repaired, errors in the process of replication, or from the insertion or deletion of segments of DNA by mobile genetic elements[7]. Mutations may or may not produce discernible changes in the observable characteristics (phenotype) of an organism. Mutations play a part in both

normal and abnormal biological processes including: evolution, cancer, and the development of the immune system, including functional diversity[4, 37].

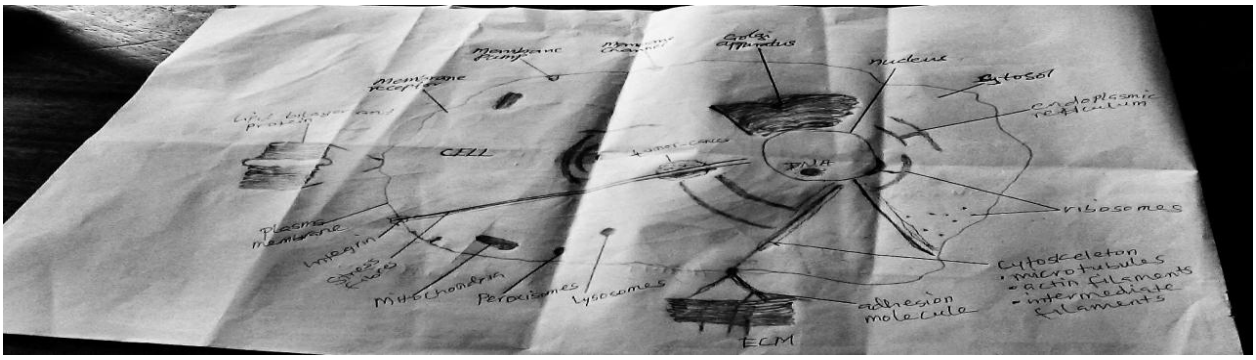


Figure 2

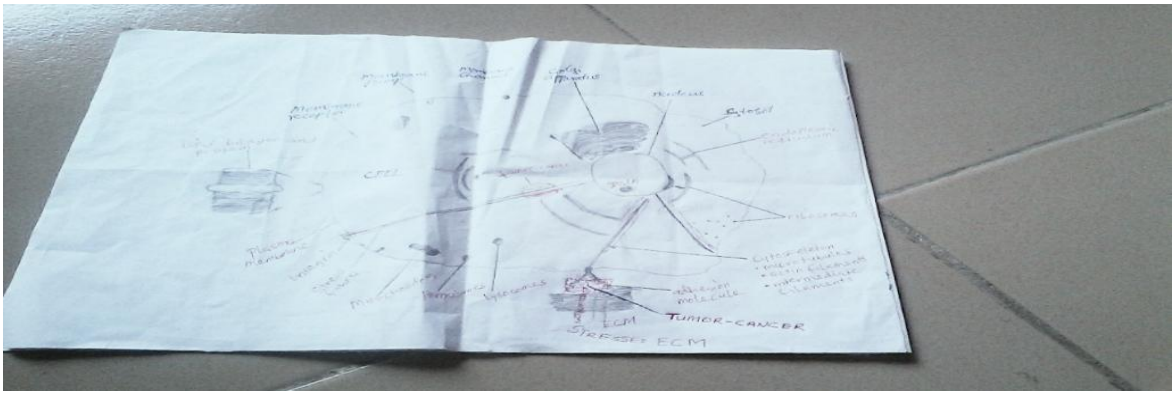


Figure 3

Figures 2 and 3: an animal cell showing stress fibres and stressed extracellular matrix that led to tumor-cancer

Figures 2 and 3 are for an animal cell. It consists of a cell membrane, a cytoplasm (i.e. fluid-like cytosol, structural cytoskeleton and dispersed organelles) and a nucleus which contains the chromosomal DNA. In the above diagram, when fibres or arteries are stressed as a result of loads applied on the body either intentionally or unintentionally, it leads to tumor – cancer. These fibres and arteries are forms of the elastic materials or soft tissue cells. The extracellular matrix (ECM) plays many functions in this study in that it is on it that the force or stress is applied which leads to tumor – cancer. The ECM gives us the viscous and elastic material or tissue as it concerns soft biological tissues in this study. It provides the tissue with strength and resilience and maintains its shape. It serves as biological active scaffolding on which cells can migrate and stick on (e.g tumor-cancer cells). It helps to regulate the phenotype of the cells. It supplies an anchor for many substances including growth factors, proteases and their inhibitors. Finally, it provides an aqueous environment for the diffusion of nutrients, ions, hormones, tumor – cancer cells and metabolites between the cell and the capillary network. Thus, the ECM regulates cell shape, orientation, movement and overall function. The cells (e.g. fibroblasts) fashion and maintain the ECM thereby

forming a strong symbiotic relationship. The ECM consists primarily of proteins (e.g. collagens, elastin, and fibronectin), glycosaminoglycans (GAGs) and bound and unbound water [11,2].

However, some scientists have carried out works on cancer but none has worked on damage mechanics model of cancer.One of these is the first applications of continuum mechanics to the study of growth in deformable tissues; a model of homogeneous stress-dependent growth for linearly elastic materials developed by [20]. Later, a continuum description of finite growth kinematics was formulated by [21,40].They examined volumetric growth, growth by accretion on surfaces and growth fields with discontinuities. In recent years, the phenomena of stress, deformation, mutation and growth in soft elastic tissue cells were of interest to several researchers [21, 14, 8, 27, 43, 32, 18, 17, 16, 35, 36]. Amongst several others, [38, 29,30,9, 24,6, 12,15, 13,28,21, 5, 34] worked on oxidative stresswhereby the mitochondrial membrane becomes permeable and the signaling cascade is triggered and cancer is the end result.

However, the works in [21] on continuum biomechanics of soft biological tissues. The study reviewed few of the many achievements in the biomechanics of soft tissues and the tools that allowed them, but, more importantly, it identified some of the open problems that merit increased attention from those in applied mechanics, biomechanics, mathematics and mechanobiology. Another work that is related to the present study under review was done by [21] on oxidative stress, disease and cancer. In this work, it showed that the ability of cells to reduce oxygen to produce energy is fundamental to aerobic life. Unfortunately, production of energy by reduction of dioxygen leads to the generation of reactive oxygen species that cause oxidative stress. It is now well established that oxidative stress causes extensive damage to cellular components, which can lead to a number of diseases, including cancer. This also provided a comprehensive review of the most up-to-date knowledge of the sources and molecular mechanisms of oxidative stress and its role in disease and cancer. The paper also focused on the novel agents and methods that can be employed to prevent oxidative stress and associated diseases in soft tissue cells.

In addition to the above elucidations, [33] in Oxidative Stress in Cancer-Prone Diseases discovered that several conditions of prooxidant states have been reported in the recent decades for a wide range of genetic diseases and provided a consistent basis for the interpretation of the phenotypes of several genetic diseases. [1] in Oxidative Stress and Breast Cancer found out that Breast cancer is the most frequently diagnosed non-skin malignancy in women in the United States, with 213,910 cases expected in [3] and its incidence is gradually increasing.Based on the above mentioned related literatures, it is observed that the effect of stress on tumor-cancer in the body of living organisms in damage mechanics has not been modeled, analyzed and proffer solutions to the related equations. Thus, these factors will modeled in damage mechanics as to expose the action of oxidative stress on the matrix wall that has tumor (voids), then how it leads to cancer and to illustrate the initiation, growth and coalescence of cancer. It is this void left by researchers and the global experience of stress and cancer that led the researcher to carry out a study geared towards damage mechanics model of cancer under oxidative stress.

N	Maximum number of cancer cell
$\boldsymbol{\sigma(x,t)}$	Stress tensor
$\boldsymbol{x}$	Position
$\boldsymbol{t}$	Time
f	Body force
$\boldsymbol{\rho(x,t)}$	Density of the ECM
$\boldsymbol{\rho_C(x,t)}$	Cell density
$\boldsymbol{\rho_{c,t}}$	Partial differentiation of cell density w.r.t, t
$\boldsymbol{\nabla}$	Laplacian operator
$\boldsymbol{n(x,t)}$	Number of cells per unit volume
$\boldsymbol{u(x,t)}$	Displacement vector of the matrix
$\boldsymbol{D_1, D_2}$	Diffusion parameters
$\boldsymbol{\mu_1, \mu_2}$	Shear and bulk viscosities of the ECM
$\boldsymbol{a_1, a_2}$	Long range effect for mechanotaxis flux
$\boldsymbol{\lambda}$	Measure of cell-cell contact activation cancer cells
$\boldsymbol{\tau}$	Cell traction force
$\boldsymbol{\theta}$	Dilation
$\boldsymbol{\varepsilon_t}$	Partial differentiation of strain tensor w.r.t. t
$\boldsymbol{\theta_t}$	Partial differentiation of dalition w.r.t. t
$\boldsymbol{u_t}$	Partial differentiation of displacement w.r.t. t (velocity of deformation of matrix)
$\boldsymbol{n_t}$	Partial differentiation of cell density w.r.t. t
$\boldsymbol{\rho_t}$	Partial differentiation of density of the ECM w.r.t. t
$\boldsymbol{\phi}$	Growth factor
$\boldsymbol{\gamma}$	Measure of the nonlocal long range cell-ECM interactions
$\boldsymbol{k}$	Rate of destruction of cells by the cancer cell
$\boldsymbol{r}$	Initial proliferative rate in cell growth
I	Unit tensor
S	Elastic parameter for the substrate attachments
$\boldsymbol{\lambda}$	Parameter that controls the activator of cancer cell growth
N	Injured area
J	The flux of cells
$\boldsymbol{J_c}$	Convective flux contribution
$\boldsymbol{J_h}$	Mechanotactic flux
E	Young's modulus
V	Poisson ratio
$\boldsymbol{\varepsilon}$	Strain

Table 1: Description of variables and parameters in the model

2 Model Formulation

From the above elucidated facts on the features of soft tissues, this study will consider damage mechanics model of cancer in the area of viscoelastic and thermo elastic constitutive relationship in its mathematics model. However, the parameters to be considered are: stress damage relation, strain –damage coupled with constitutive equation and law of elasticity coupled with damage, viscoelastic tensor equation, mechanotaxis equation with mitosis M and conservation equation for the matrix material. From all indications, the model equation will show three equations; such as the Force Balance Equation, Cell Conservation Equation and the Matrix Conservation Equation respectively.For soft tissues, a linear viscoelastic material gives the stress–strain constitutive relation below which is the usual equation for a linear viscoelastic material [25, 31] that supports the equations below.

$$\mu_1 \frac{\partial^2 \varepsilon}{\partial x_i \partial t} + \mu_2 I \frac{\partial^2 \theta}{\partial x_i \partial t} + \frac{\partial \varepsilon}{\partial x_i} + \nu' I \frac{\partial \theta}{\partial x_i} + \frac{\left(\frac{\partial \rho}{\partial x_i}\right) \pi I\left(\frac{\partial n}{\partial x_i}\right)}{\left(1+\lambda n^2\right)} + \frac{\tau\left(\frac{\partial n}{\partial x_i}\right) \gamma I\left(\frac{\partial \rho}{\partial x_i}\right)}{\left(1+\lambda n^2\right)} . = s\rho u \qquad (1)$$

$$\frac{\partial \rho_c}{\partial t} = D_1\left(\frac{\partial^2 n}{\partial x^2}\right) - D_2\left(\frac{\partial^4 n}{\partial x^4}\right) - a_1\left(\frac{\partial n}{\partial x} + \frac{\partial^2 \rho}{\partial x^2}\right) + a_2\left(\frac{\partial n}{\partial x} + \frac{\partial^4 \rho}{\partial x^4}\right) - \nabla \bullet \left(n u_t\right) + rn\left(N - n\right) \qquad (2)$$

$$\frac{\partial \rho}{\partial t} + u_t\left(\nabla \bullet \rho\right) + \rho \bullet \left(\nabla u_t\right) = 1 - \nu\theta \qquad (3)$$

From the above model equations (1), (2) and (3) for the study, we have three dependent variables which are the density fields $\rho_C(x,t)$, $\rho(x,t)$and the displacement field $u(x,t)$. The parameters involved are $D_1, D_2, a_1, a_2, \mu_1, \mu_2, r, N, \tau, \lambda, \gamma, s, E \text{ and } \nu$,where matrix flux is taken to be through convection and $S(n,\rho,u) = 1 - \nu\theta$ is taken to be the rate of secretion or spread in matrix by the cancer cells. Upon expansion with the product rules for vector calculus the above field equations are expressed as equation 1 – 3. However, to evaluate the relative importance of the various effects of the variables used in the study, we nondimensionalised the equations for simplicity of analysis.

Hence, using general length (L) and timescales (T), and for uniform initial matrix density (ρ_0). Setting $r^* = \frac{r}{L}, t^* = \frac{t}{T}, n^* = \frac{n}{N}, u^* = \frac{u}{L}, \rho^* = \frac{\rho}{\rho_0}, \nabla^* = L\nabla, \theta^* = \theta, \varepsilon^* = \varepsilon, \gamma^* = \frac{\gamma}{L^2},$

$r^* = rNT, S^* = \frac{s\rho_0 L^2(1+\nu)}{E}, \lambda^* = \lambda N^2, \tau^* = \frac{\tau \rho_0 N(1+\nu)}{E}, a_1^* = \frac{a_1 \rho_0 T}{L^2}, a_2^* = \frac{a_2 \rho_0 T}{L^4},$

$i = 1,2, N_i^* = \frac{N_i(1+\nu)}{TE}, D_1^* = \frac{D_1 T}{L^2}, D_2^* = \frac{D_2 T}{L^4}$ (4)

The parameters have reduced to 12 parameters. If we consider T as the mitotic time (proliferation time for cancer cells) to be $\frac{1}{rN}$, then $r^* = 1$ because of our interest on the proliferation rate of cancer cells on the time scale. Conversely, we can also consider T so that $\gamma^* = 1$ or $\mu_i^* = 1$; for $i = 1$ or $i = 2$. Similarly, consider a relevant length scale for further reduction of the number of parameter groupings depending on what timescale and length scale we are concern with.
However, with this nondimensionalisation in (4) above and upon dropping the asterisks parameters for simplicity we have equations (5), (6) and (7) which can be solved by using the method of travelling wave solution.

$$\rho_{c,t} = D_1\nabla^2 n - D_2\nabla^4 n - \nabla.\left[a_1 n\nabla\rho - a_2 n\nabla\left(\nabla^2\rho\right)\right] - \nabla.\left(nu_t\right) + rn\left(N-n\right) \quad (5)$$

$$\nabla\cdot\left\{\left(\mu_1\varepsilon_t + \mu_2\theta_t I\right) + \left(\varepsilon + \nu'\theta\mathbf{I}\right) + \frac{\pi n}{1+\lambda n^2}\left(\rho + \gamma\nabla^2\rho\right)\mathbf{I}\right\} = s\rho u \quad (6)$$

$$\rho_t + \nabla\cdot\left(\rho u_t\right) = 1 - \nu\theta \quad (7)$$

All the dimensionless parameters are positive; where $a_1, a_2, D_1, D_2, r, \tau, \lambda$ are associated with the cell properties and $\mu_1, \mu_2, \nu', \gamma, s$ are related to the matrix properties.

Then, graphically the effect of strain and stress (damage) on the ECM can be represented below:

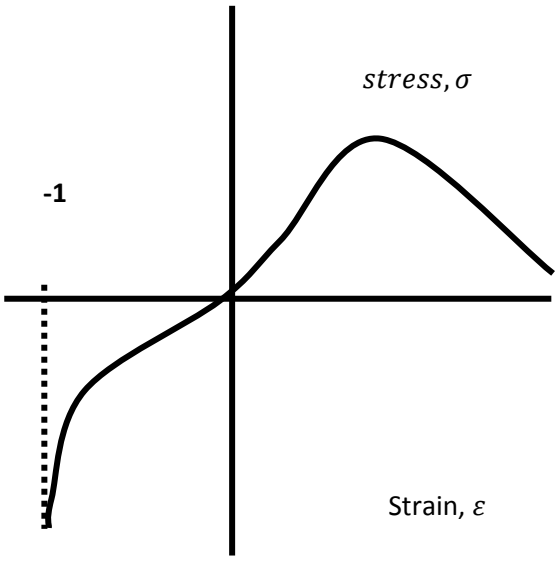


Figure 4: The effect of straining extracellular matrix is to align the fibres and stiffen the material (which leads to tumor cells). it increases with strain until the yield point levels off and drops for large strains as the material tears (cancer cells). Adopted from [31].

2.1 Acha-ero

The model for this study is the above three equations (equations 5, 6 and 7) which is seen or noticeable in a real life situation in a disease called "Acha–ero" or "Nshi–calabar". Acha-Ero is a disease found in the Eastern and Southern part of Nigeria. This "Acha–ero" disease proves that the movement of the cancer cell is from one position to another on daily basis. "Acha–ero" also supports that the movement of the cancer cells in a steady state. This "Acha–ero" starts in the form of a boil or when sharp object pierces into the legs or any parts of the body of an organism thereby forming growth (Tumor) associated with pains. At a point, the open wound starts to form internal bleeding or clotted blood that continues to grow steadily to a certain point when the tip will become very reddish in colour with a whitish substance (puse) which is ready to burst on its own or someone has to burst it open and it will spread with time. However, when this growth or wound is opened, it secretes a lot of fluids which activate the rate of spread with time from one position to another. "Acha–ero" usually starts at a point (position) and with time it displaces to more points.

This leads us to the assumption of the initial boundary condition as $u=1, \rho_C = 1, \rho = 1$ and that position (x) changes with time (t) which we considered as a constant. Since the position of Acha – Ero in the body starts at a point which could be any positive real number (constant) such as 1, 2, 3, …. Thus we put $\frac{\partial u}{\partial t} = 1$ because equation (7) shows how dense the cancer cells are packed in the matrix. Equation (7) is an inhomogeneous partial differential equation which can be solved by using the travelling wave method of solution. This travelling wave method of solution is suitable because cancer cells move and also has a viscous property. From equation (7), there is no convective flux or motion. Hence, $\nabla \bullet (\rho u_t) = 0$; therefore equation (7) reduces to

$$\rho_t = 1 - \theta\nu \qquad (8)$$

Integrating w.r.t. x, t yields

$$\rho = t - 3\nu x_i t + \frac{3}{2}\nu k t^2 . \qquad (9)$$

Similarly, to solve for $\rho_c(x,t)$ upon integration using equation (5) gives

$$\rho_c = 3D_1 t\left(x_i - \frac{kt}{2}\right) - 3D_2 t\left(x_i - \frac{kt}{2}\right) - 3a_1\nu\left(\frac{x_i^2 t^2}{2} - \frac{3x_i kt^3}{2\bullet 3} + \frac{k^2 t^4}{2\bullet 4}\right) - 3a_2\nu\left(\frac{x_i^2 t^2}{2} - \frac{3x_i kt^3}{2\bullet 3} + \frac{k^2 t^4}{2\bullet 4}\right)$$
$$- 3k\left(\frac{x_i^2 t^2}{2} - x_i kt^2 + \frac{kt^3}{3}\right) - 3kt\left(x_i - \frac{kt}{2}\right) + rNt\left(x_i - \frac{kt}{2}\right) - r\left(\frac{x_i^2 t^2}{2} - x_i kt^2 + \frac{kt^3}{3}\right) \qquad (10)$$

Finally, to solve for $u(x,t)$ by integrating w.r.t x, t using equation (6) and its expansion using vector calculus and the same travelling wave method of solution yields

$$u(x,t)=\frac{-3k\left(\chi_i^2-2x_ikt+k^2t^2\right)\left(\mu_1+\mu_2I\right)+3\left(x_i-kt\right)\left(1+\nu I\right)-\dfrac{27\tau\nu tI\left(x_i-\dfrac{3x_ikt}{2}+\dfrac{k^2t^2}{2}\right)}{1+\lambda\left(\chi_i^2-2x_ikt+k^2t^2\right)}\left(1+\gamma\right)}{s\left(t-3\nu tx_i-\dfrac{3\nu kt^2}{2}\right)} \tag{11}$$

Thus, the solutions to our mathematical model of Damage Mechanics Model of Cancer are the equations (9), (10) and (11) which shows that the Extracellular Matrix density $\rho(x,t)$, cell density $\rho_c(x,t)$ and Cell Displacement $u(x,t)$are functions of position and time respectively. From all indications, the solutions to the model equations showcased a steady state solution showing that the cancerous cells are proliferating by defiling all medications and they are exponentially growing with time.

3 Analysis of Model

From the above elucidations, three systems of equation for the model which comprises the cell conservation equation which is cell density, $\rho_c(x,t)$ as equation (5), the displacement, $u(x,t)$ given as equation (6) and the equation for the matrix material $\rho(x,t)$ which is the matrix density is given by equation (7). The stability analysis will be determined using the same three equations (5 -7) respectively.

3.1 Equilibrium Analysis

The first step to a qualitative analysis is finding the equilibria of the model. Equilibrium solutions are ones that do not change with time, so the partial derivatives are equal to zero. Thus, to model the spread of cancer cells growing in a solid tumor–cancer called Acha–ero as observed in the equation system (5), (6) and (7). The researcher must admit the spread in equation (9), (10) and (11) solutions. Considering the complexity in cancer cells reproduction and proliferation with the experience gained from the model solutions of this study. Thus, to find useful analytical solutions to this nonlinear systems of equation by setting: ρ_{ce}, u_e and ρ_e to be the equilibrium solutions for the cell density(5), displacement (6) and matrix density (7) respectively then let $n=\rho_{ce}$ in equation (5).

One of the equilibria solutions is a trivial solution with non-existence of the density fields (cell density and matrix density) and the displacement giving:

$$\left(\rho_{ce},u_e,\rho_e\right)=\left(0,0,0\right) \tag{12}$$

The other equilibrium solution shows the existence of both cell density and displacement but there is no matrix density which satisfies:

$$(\rho_{ce}, u_e, \rho_e) = \left(N, \frac{\nabla \bullet \varepsilon + \nu I \nabla \bullet \theta}{s}, 0 \right) \quad (13)$$

3.2 The Stability

In solving for the stability, this can be determined by performing a linearization to find the growth rate, ϕ of cancer cells in the body of the organisms, traction factor A, stress factor B, diffusion factor C, haptotaxis or mechanical factor D (movement of the cancer cells) and the secretion factor E; all are functions of k in the model equations. Hence, the linear stability of the solution is obtained by seeking solutions of the linearised equations (5) – (7) and writing it in the corresponding variables as below gives

$$\left(\rho_{c,t} - D_1\nabla^2 n + D_2\nabla^4 n - rNn + rn^2\right)\rho_c + \left(a_1 n\nabla^2\rho + a_2 n\nabla^4\rho\right)\rho + \left(\nabla \bullet (nu_t)\right)u = 0 \quad (14)$$

$$\left(\frac{\tau\rho\nabla \bullet n}{1+\lambda n^2}\right)\rho_c + \left(\frac{\varpi n\nabla \bullet \rho I}{1+\lambda n^2} + \frac{\varpi n\gamma\nabla^3\rho I}{1+\lambda n^2}\right)\rho + \left(\mu_1\nabla \bullet \varepsilon_t + \mu_2\nabla \bullet \theta_t I + \nabla \bullet \varepsilon + \nu'\nabla \bullet \theta I - s\rho u\right)u = 0 \quad (15)$$

$$(\nu\theta - 1)\rho_c + (\rho_t)\rho + \left(\nabla \bullet (\rho u_t)\right)u = 0 \quad (16)$$

$$\frac{\partial}{\partial t} = \phi, \nabla = ik, \rho_c = 1,\ \rho = 1,\ u = 1,\ I = 1,\ , \quad (17)$$

Since this study is carried out in the three dimensional space, the analysis will be limited to x_i direction because of the consideration of the growth rate ϕ and destruction rate of cells by the cancer cell, k, where $\rho_{c,t}, \theta_t, u_t, \rho_t, \varepsilon_t$ are in their partial derivatives form and are equal to ϕ,

$$\tau_1 = \frac{\tau}{1+\lambda},\ \tau_2 = \frac{\tau}{1+\lambda n^2},\ \ \mu_1 + \mu_2 = \mu \quad (18)$$

Thus, considering $\rho_c - 1$, $\rho - 1$ and u small, upon substituting into the nonlinear system of equation and keeping the linear terms in $\rho_c - 1$, $\rho - 1$ and u, and their derivatives gives the linear system of equations (14) – (16) above where $\lambda < 1$, $\tau_2 > 0$, and λ is a measure of cell –cell contact activation of cancer cells and also nonnegative. In solving equations 14 -16 using determinant method gives

$$\begin{vmatrix} \phi + D_1k^2 + D_2k^4 - rN + r & -a_1k^2 + a_2k^4 & ik\phi \\ ik\tau_2 & ik\tau_1 - ik^3\gamma\tau_1 & -2\mu k^2\phi - (1+\nu')k^2 - s \\ (\nu\theta - 1) & \phi & ik\phi \end{vmatrix} = 0 \quad (19)$$

In the determinant above, we considered our solutions in the growth rate ϕ as a function of rate of destruction of cells by the cancer cell k^2, traction factor A, stress factor B, diffusion factor C, haptotaxis or mechanical factor D (movement of the cells) and the secretion factor E in the model

equations. Thus, we put $A = \tau_1 - \gamma\tau_1 k^2$, $B = \left(1 + \nu'\right)$, $C = D_1 + D_2 k^2$, $D = k^2\left(a_2 - a_1\right)$ and $E = \left(\nu\theta - 1\right)$ so that equation (19) yields the graphical discussions below.

The equations with ϕ give us steady state solutions which means that the secretion surface is activating the rate of growth or proliferation of cancer cells in the body of the organism. This stable solution is an indication of the presence of cancer cells which is in a steady state growth showing that the cancerous cells have defiled all medications because of the action of the oxidative stress. These results also established that there is presence of oxidative stress in the injured area which is also acting as an activator to the proliferation rate of the cancerous cells showing that the immune system is weak.

4 Simulation of Model

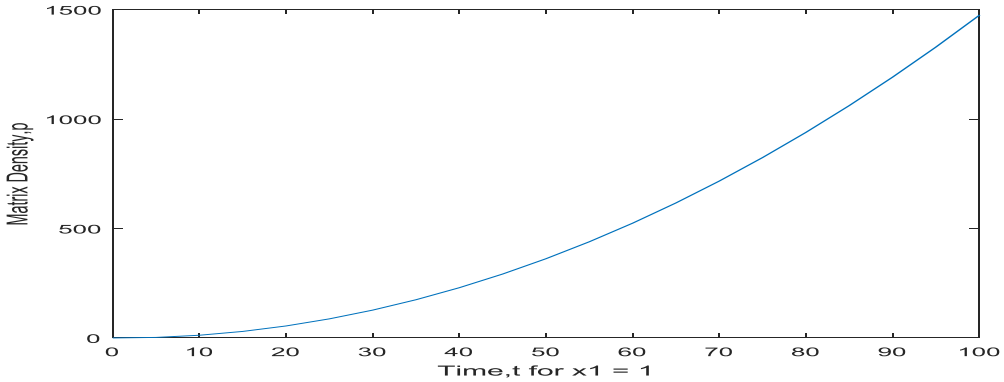


Figure 5: Values : $\nu = 0.2$, $X_1 = 1$, $k = 0.5$, $t = 0:5:100$

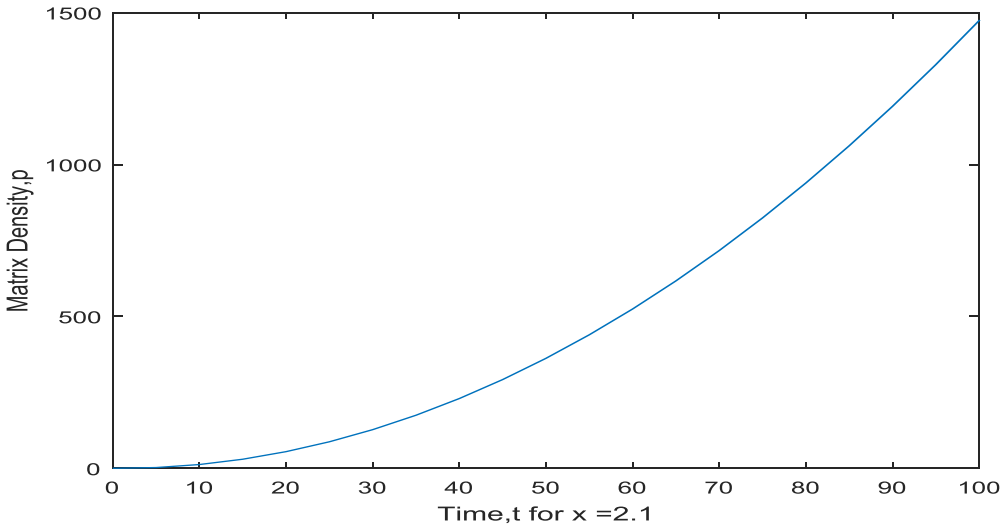


Figure 6: Values : $\nu = 0.2$, $X_1 = 2.4$, $k = 0.5$, $t = 0:5:100$

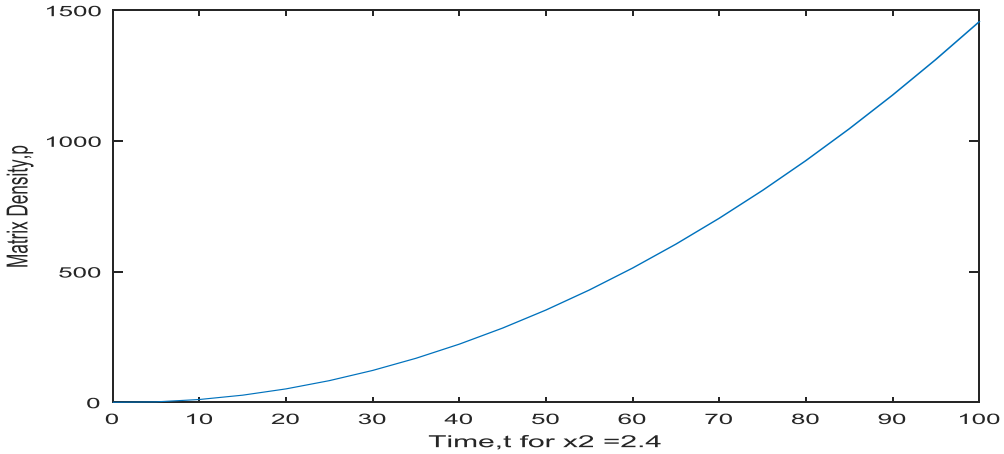


Figure 7: Arbitrary Values: $\nu = 0.2$, $x_3 = 2.4$, $k = 0.5$, $t = 0:5:100$

Figure 5 - 7 end result shows the matrix density, ρ against time, t in days with arbitrary values of x_1, x_2 and x_3 respectively. The graph portrays that the matrix is quadratic in t. The existence of cancer cells in the matrix gives rise to exponential rise in the time taking for the density to increase. In terms of the time, it shows that the lower the time the lower the matrix density and as the time increases the cancer cells in matrix density also increases. From figure 5 to 7, also depicts that an increase in the number of cancer cells leads to an increase in the matrix density of the organism and an increase in the time for the oxidative stress to lose its bonding leads to an increase in the cancer cells to proliferate and spread at different time interval which in turns increases the population size of cancer cells and the matrix enlarges with time; and vice versa. The figures are also telling us that when matrix volume is 50, the time is 10days; taking the ratio gives 5:1 and when the density increased to 100:20 the ratio becomes 10:2.

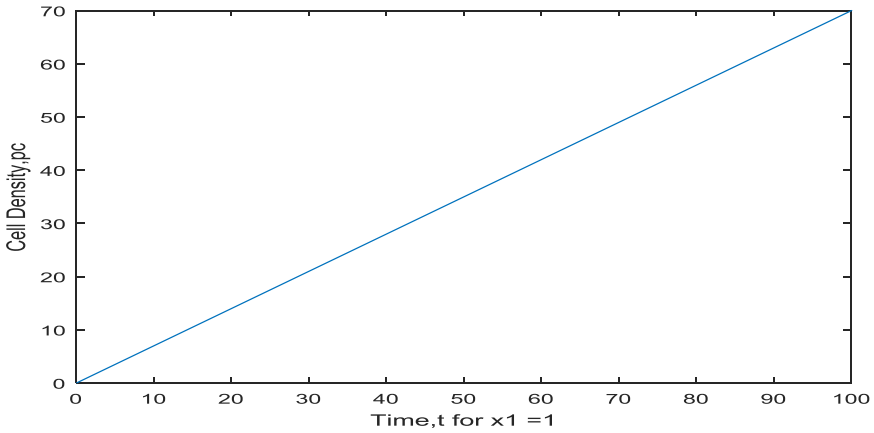


Figure 8: Arbitrary Values: $D_1 = 1$, $D_2 = 0.6$, $\chi_1 = 1$, $k = 0.5$, $r = 0.8$, $N = 1$, $t = 0:5:100$

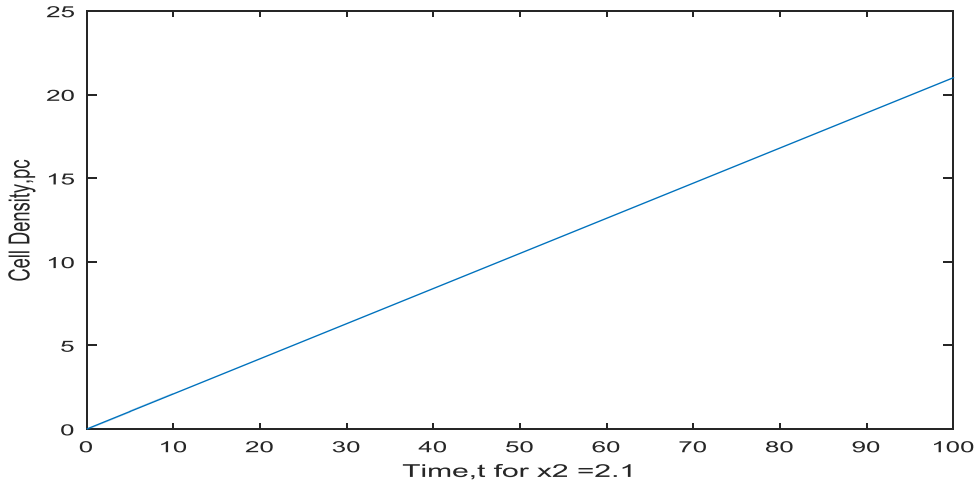


Figure 9: Arbitrary Values: $D_1 = 1$, $D_2 = 0.6$, $\chi_2 = 2.1$, $k = 0.5$, $r = 0.8$, $N = 1$, $t = 0:5:100$

Figure 8 and 9 is the graph of cell density against time; this is showing the change in the cell density with time. The two figures are showcasing that the cell density at different values of position (x_1, x_2, x_3) which linearly increases as the time increases. The figures are also depicting the effects of oxidative stress, temperature and traction force with time taken (in days) in the matrix of the organism revealing that the volume of cancer cells have increased as the matrix harbours more cancer cells. These figures explain the intensity of the oxidative stress action in growing the cancer cells thereby making it to be densely packed and are linearly directly to the time in days it takes to spread or proliferate in the matrix of an organism. The graph portrays that the oxidative stress has lost its bonding and its action in the body of the organism shows up by growing and packing the cancer cells in the matrix in a linear direction.

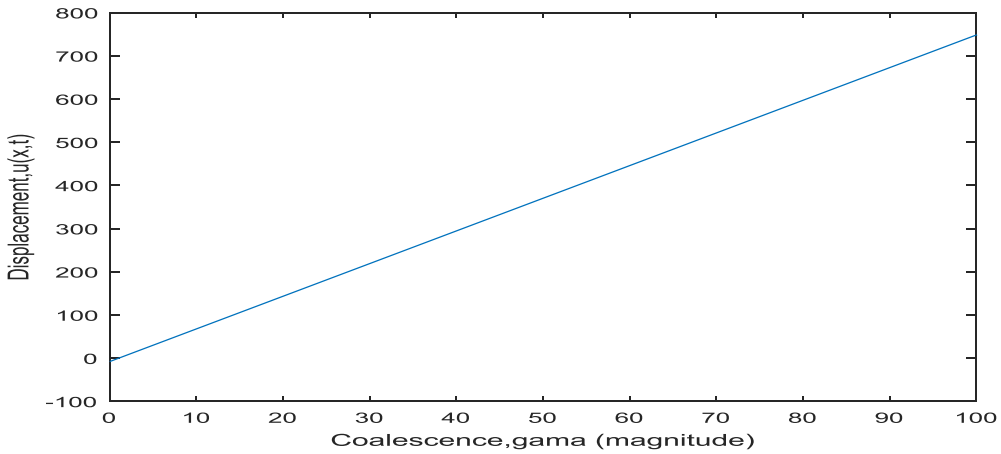


Figure 6: Arbitrary Values: $\mu_1 = 1$, $\mu_2 = 0.4$, $\chi_1 = 2.1$, $k = 0.5$, $\tau = 0.7$, $I = 1$, $\gamma = 0:5:100$ $\lambda = 0.5$, $s = 10^6$, $\nu = 0.2$, $r = 0.8$, $N = 1$, $t = 2$

Figure 6 showcases the displacement against coalescence time in days (magnitude) of the wound in the matrix of the organism. This figure explains that the position, size and direction of the cancer cells is linearly directly to the time in days it takes to spread or proliferate and coalescence in the matrix of an organism. The graph also reveals that the oxidative stress has lost its bonding and its action in the body of the organism which displays up by growing and spreading the cancer cells in the matrix in a linear direction. Here, the oxidative stress action is on the increase showing that the cancer cells have defiled all medications, they are densely packed and then reproducing and proliferating in the matrix. In terms of the temperature and traction force which causes the wound to dilate, it shows that the lower the temperature of matrix, the lower the oxidative stress in the matrix density that can cause displacement and coalescence; and as the temperature and traction force increases the oxidative stress in matrix density also increases which leads the cancer cells to reproduce beyond measure and expand their position above measures. The figure is also telling us that when the cells are densely packed in matrix it causes a rise in temperature, traction force and matrix density which allows displacement to take place. Thus, it is the action of oxidative stress that leads to displacement and coalescence of the cancer cells. There is no displacement and coalescence at point (0,0) because the wound is still in its solid tumor state.

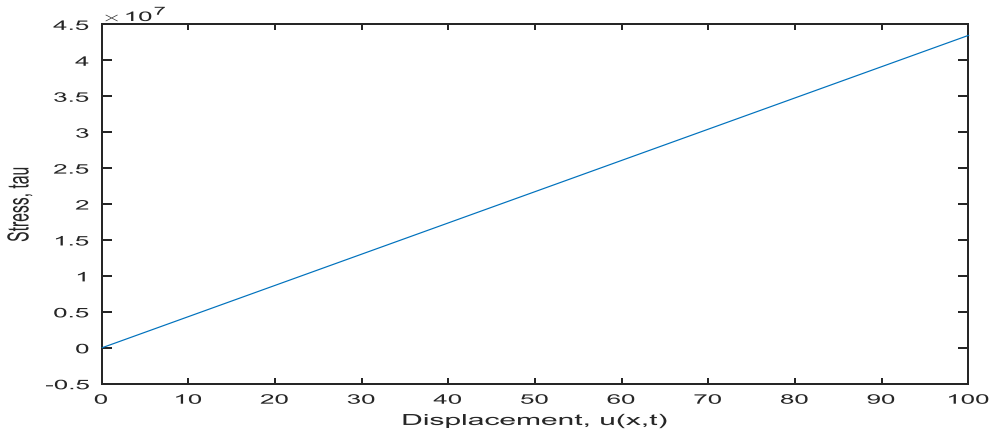


Figure 7: Arbitrary Values: $\mu_1 = 1$, $\mu_2 = 0.4$, $\chi_1 = 2.1$, $k = 0.5$, $\tau = 0.7$, $I = 1$, $u = 0:5:100$ $\lambda = 0.5$, $s = 10^6$, $\nu = 0.2$, $r = 0.8$, $N = 1$, $t = 2\sec s$, $\gamma = 0.7$

Above is the graph showing the action of oxidative stress in the displacement of the cancer cells in the body of the organisms (matrix). This is showcasing that the oxidative stress action at position (x1, x2, x3) linearly increases as the cancer cells increases and changes position. Figure 7 depicts the effects of oxidative stress against displacement of cancer cells (in days) in the matrix of the organism which makes the matrix volume to increase as to enable it harbour cancer cells. This figure explains the intensity of the oxidative stress action on the cancer cells displacement at zero is minimal because there is no wound for it to act upon. The oxidative stress action is on the high side and become linear in growth as the displacement increases from position one (x_1, x_2, x_3) to infinity with time it takes to spread or proliferate in the matrix. The graph also portrays that the oxidative stress has lost its bonding and its action in the body cells of the organism shows up by growing the cancer cells in the matrix in a linear direction. Hence, the oxidative stress values is on the increase showing that the cancer cells have defiled all medications, they are densely packed and it has started changing its position in the matrix wall of the organism. The oxidative stress action in the extra-cellular matrix begins to lose its bonding at point (0,0) which illustrate that there is tumor present in the body that will initiate cancer cells in progression to coalescence and then proliferate.

Other models that support this study is the model of stress tensor which consists of the ECM and the cell parts. The graph below shows the Extra Cellular Matrix part of the oxidative stress against time.

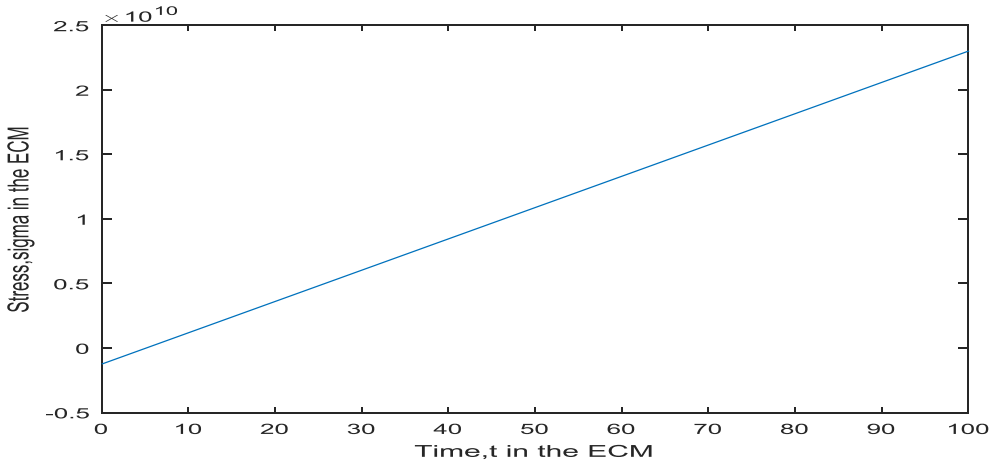


Figure 8: Values: $\tau = 0.7$, $\rho = 1.2 \times 10^{-2}$, $\lambda = 30$, $I = 0.3$, $\chi_1 = 2.1$, $\chi_2 = 2.4$, $\chi_3 = 3.0$, $k = 0.5$, $t = 0:5:100$

Figure 8 depicts the effects of oxidative stress against time taken (in days) in the matrix of the organism for the volume to increase as to harbour cancer cells. This figure explains the intensity of the oxidative stress action on the cancer cells is on the high side and it is linearly directly to the time in days it takes to spread or proliferate matrix of the organism.

The graph portrays that the oxidative stress has lost its bonding power and its action in the body of the organism shows up by growing the cancer cells in the matrix in a linear direction. Hence, the oxidative stress values is on the increase showing that the cancer cells have defiled all medications and they are densely packed in the matrix. The existence of oxidative stress in the matrix gives rise to a linear increase in the time for cancer cells coalescence as the time in day and cell displacement increase. In terms of the presence of temperature and traction force, it shows that the lower the oxidative stress of matrix, the lower the temperature and traction force in the matrix density that can cause coalescence and as the temperature increases the oxidative stress in matrix also increases which leads the cancer cells to reproduce beyond measure. The figure is also telling us that when the cells are densely packed in matrix it causes a rise in temperature, traction force and matrix volume; thus, the action of oxidative stress that leads to coalescence of cancer cells. The oxidative stress action in the extra-cellular matrix begins at some point with a negative value which shows that it has lost its bonding and at point (0,0) it shows there is no cancer cell and coalescence then it is in tumor state. Hence, the model solution also ascertained that it took between 80 -100days for the stress to act on a tumor tissue before it ruptures.

Considering that the cancer cells are densely packed; we have Stress in the cell against time as below:

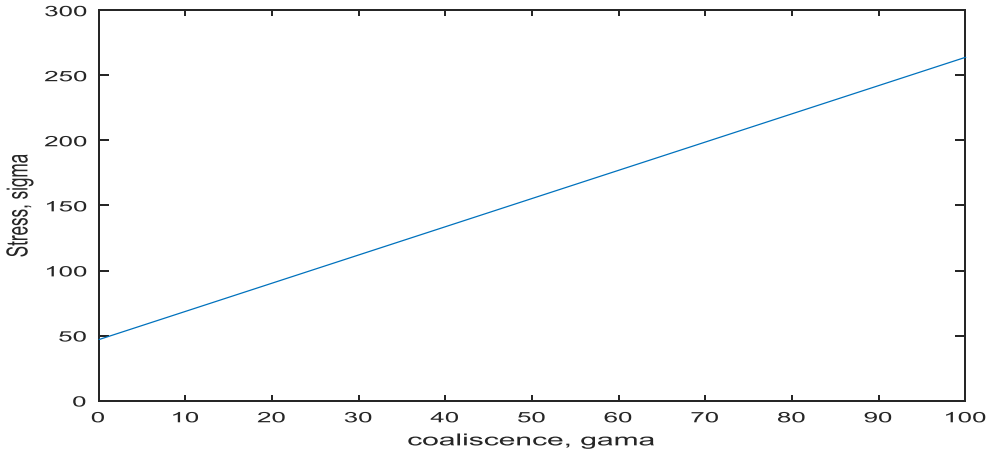


Figure 9: is a graph showing the amount of oxidative stress that leads to coalescence of the cancer cells. Arbitrary Values: $\tau = 0.7$, $\rho = 1.2 \times 10^{-2}$, $\lambda = 30$, $I = 0.3$, $\chi_1 = 2.1$, $\chi_2 = 2.4$, $\chi_3 = 3.0$, $k = 0.5$, $t = 2\sec s$, $\gamma = 0:5:100$

Figure 9 showcases the oxidative stress against coalescence time in days in the matrix of the organism. This figure explains the intensity of the oxidative stress action on the cancer cells is on the high side and it is linearly directly to the time in days it takes to spread or proliferate matrix of the organism.

The graph portrays that the oxidative stress has lost its bonding and its action in the body of the organism shows up by growing the cancer cells in the matrix in a linear direction. Hence, the oxidative stress values are on the increase showing that the cancer cells have defiled all medications and they are densely packed in the matrix. The existence of oxidative stress in the matrix gives rise to a linear increase in the rate of cancer cells coalescence as the time in day and cell displacement increase. In terms of the temperature, it shows that the lower the temperature of matrix, the lower the oxidative stress in the matrix density that can cause coalescence and as the temperature increases the oxidative stress in matrix density also increases which leads the cancer cells to reproduce beyond measure. The figure is also telling us that when the cells are densely packed in matrix it causes a rise in temperature, traction force and matrix volume; thus, the action of oxidative stress that leads to coalescence is at point 50 and at point (0,0) there is no coalescence then it is tumor state. However, analytic solution showed that the magnitude of stress that led the tumor to rupture was $250KN$ and the time taken to rupture was 100days.

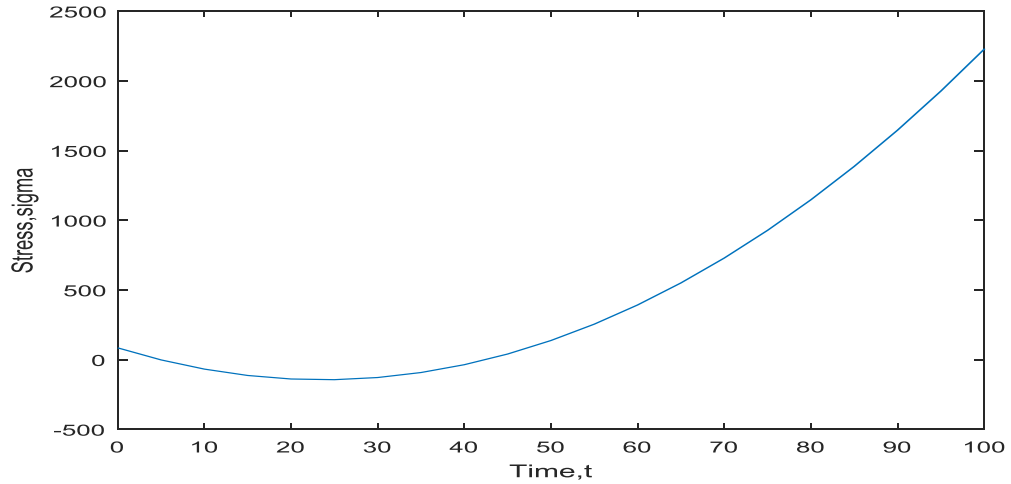


Figure 10: Values: $\tau = 0.7$, $\rho = 1.2 \times 10^{-2}$, $\lambda = 30$, $I = 0.3$, $\chi_1 = 2.1$, $\chi_2 = 2.4$, $\chi_3 = 3.0$, $k = 0.5$, $\gamma = 0.5, t = 0:5:100$

Figure 10 end results shows the amount of oxidative stress, σ in the cell against time, t in days with arbitrary values of x_1, x_2 and x_3 respectively that leads to cancer. The graph portrays that the oxidative stress is quadratic in t. The graph depicts the existence of cancer cells in the cell gives rise to exponential rise in the time taking for oxidative stress to lose its bonding in body of the organism to increase which increases the cancer cells proliferation. In terms of the time, it shows that the lower the time in days the lower the oxidative stress action and as the time increases the action of oxidative stress on cancer cells proliferation increases. Thus, the model result illustrated that the amplitude of stress in the tumor that led to coalescence was $2000KN$ and the time taken to coalescence was 100days.

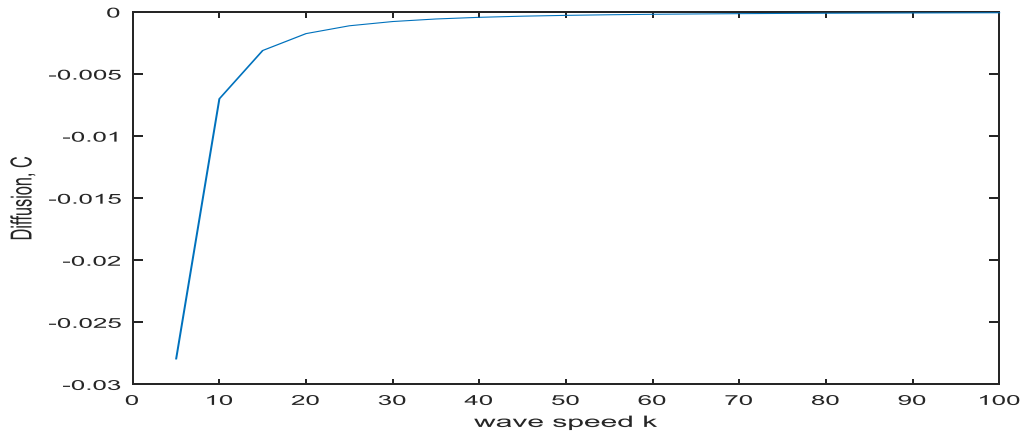


Figure 11a above is showing the action of diffusion at the injured area with Arbitrary Values: $k = 0:5:100$, $\phi = 0.7, r = 0.8$, $N = 1$.

For $N = 0$ implies that it is no open wound yet and that gives the equation below and figure 11b:

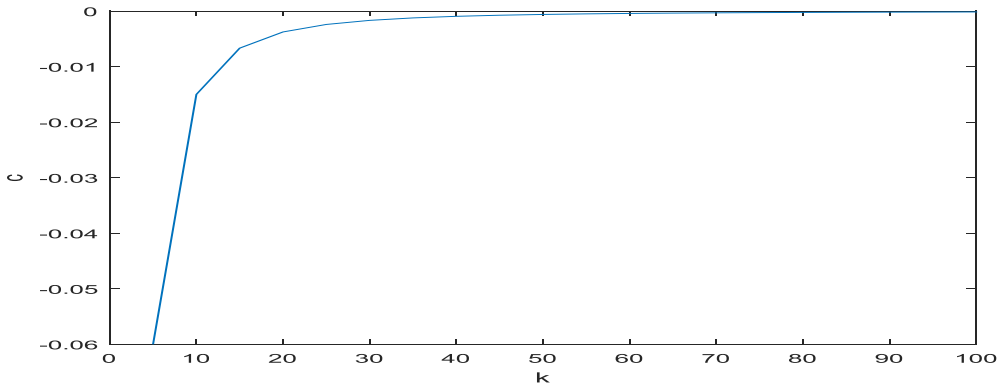


Figure 11b Arbitrary Values: $k = 0:5:100$, $\phi = 0.7$, $r = 0.8$

Figure 11a &b is a graph showing the action of diffusion against the rate of destruction of cells by the cancer cell (k) of the cancer cells in the body of the organisms. This is showcasing that when the oxidative stress action is at its maximum peak at position (x1, x2, x3), it asymptotically penetrating deep into the body of an organism and constant at some point thereby increasing the rate of destruction of cells around the surrounding environment in which cancer cells proliferate by damaging the cells within the region and change position of the cells. Figure 11 outcome is the graph showcasing the diffusion, C of the cancer cells against the rate of destruction of cells by the cancer cell, k. The graph is opposite of figures 1 to 3 because it shows an asymptotical behaviour that the cancer cell diffusion rate is in an increasing amplitude as the rate of destruction of cells by the cancer cell, k increases and digs deep into the matrix system of the organism; thereby increasing the growth and proliferation of cancer cells. This graph portrays that as the cancer cells are diffusing, it gets to zero point and stops as the destructive parameter increases. The presence of diffusion and destructive parameter leads the cancer cells to exhibit an asymptotical growth in the body as seen in the figure above. In terms of the spread, its harm is directly done by the action of oxidative stress losing its bonding from the body system of the organism in question while in turns causes matrix to enlarge beyond measure which is seen in the Acha-Ero disease; as its immune system is being destroyed that leads to the death of the organism from the competition.

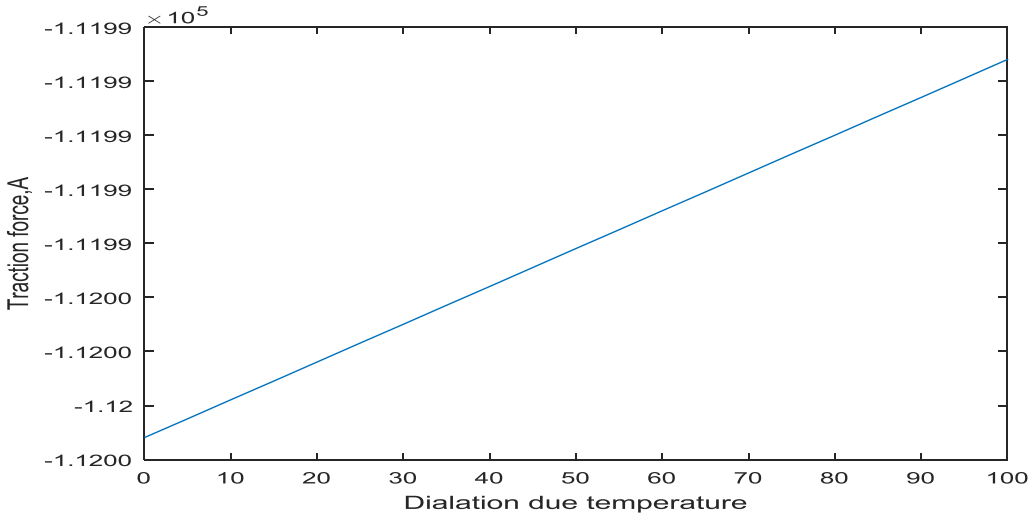


Figure 12 is depicting the action of traction force, A against dialation rate due to temperature with arbitrary values: $A = \gamma\tau_1 k^2 - \tau_1$, with $\gamma = 0.5, \tau_1 = 0.7\ \phi = 0.7, s = 0.8$, $\mu = 7\times10\text{^}7$, $\theta = 0:5:100\ N = 1, r = 0.8, \phi = 0.7, \nu = 0.2, \theta = 30^0, D_1 = 0.2, D_2 = 0.6, k = 0.5$

Figure 12 analyses the Traction force, A against dilation (theta) in the matrix density. This figure explains that the intensity of the traction is negative and linearly directly to the rate of dilation of the cancer cells in the matrix of the organism.

The graph portrays that the traction force acting upon the cancer cells in the matrix is linear in theta, θ. Hence, the traction force negative values show that the cancer cells have defiled all medications and are densely packed in the matrix. The existence of traction force on cancer cells in the matrix gives rise to a linear increase in the rate of dilation as the time in day and cell displacement increase. In terms of the temperature, it shows that the lower the temperature the lower the traction force in the matrix density and as the temperature increases the cancer cells in matrix density also increases. From figure 12, it depicts that an increase in the number of cancer cells leads to an increase in the temperature and traction force of the matrix density of the organism; and an increase in the time for the oxidative stress to lose its bonding leads to an increase in the action of traction on the cancer cells to proliferate and spread at different time interval which in turns increases the population size of cancer cells, positions and the matrix enlarges with time. The figure is also telling us that when the cells are densely packed in matrix it causes rise in temperature and matrix volume; thus, density increases to 100:20 the ratio becomes 10:2. The figure showed that the environmental factor that affected the tumor that led to rupture was temperature given as θ between $85^0 - 100^0$ c.

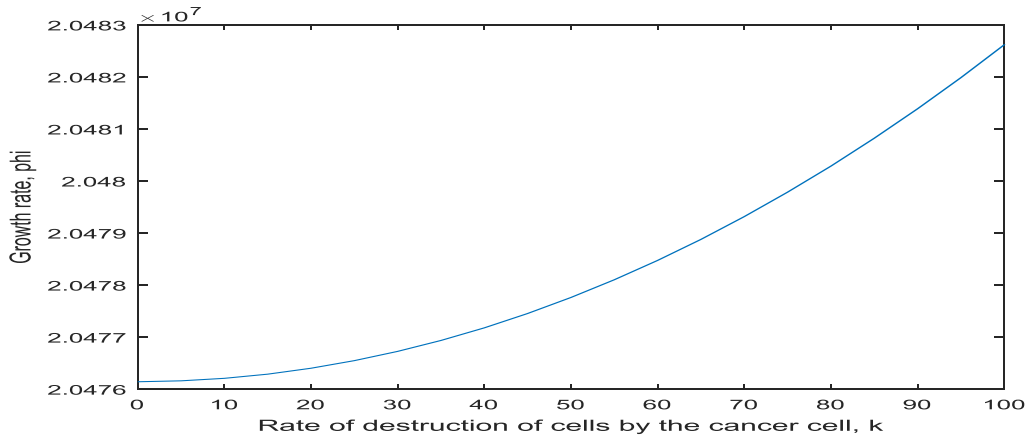


Figure 13Arbitrary values: $A=\gamma\tau_1 k^2-\tau_1$, with $\gamma=0.5, \tau_1=0.7, \mu=7\times10\text{^}7$, $B=\left(1+\nu^t\right)=14.3333$, $k=0:5:100$

Figure 13: the graph above is showing the growth rate of cancer cells (proliferation rate) against the rate of destruction of cells by the cancer cell, (k^2) and how the cancer cells are spreading in the body of the organisms. This is showcasing that when the oxidative stress action is at its maximum peak at position (x1, x2, x3), it exponentially penetrates deep into the body of an organism thereby increasing the wave speed in which cancer cells proliferate and change position (that in increase in the matrix density). Figure 13 end result shows the growth rate of cancer cells, ϕ against the destructive rate of cells by the cancer cell, k^2 with arbitrary values of other parameters. The graph portrays that the growth rate is quadratic in k. When the growth rate and the rate of destruction is at the point (0,0) it signifies no cancer which shows tumor stage otherwise, it is full blown cancer as found in Acha-Ero disease. From figure 13, it depicts that an increase in the number of cancer cells leads to an increase in the matrix density of the organism and an increase in the time for the oxidative stress to lose its bonding leads to an increase in the cancer cells to diffuse deep, grow, proliferate and spread at different time interval and positions which in turns increases the population size of cancer cells and the matrix enlarges with time; and vice versa. The figure is also telling us that when matrix volume increases, the viscous nature speeds up the growth and displacement of cancer cells as the time in days also increases.

5 Discussion of Results

The changes in tumor growth as a result of oxidative stress into cancer for this study is described by the mathematical model solutions given in equations 9, 10 and 11 above which shows the initiation, evolution and proliferation of cancer cells in a diffusive state. At this moment, the three system of equation depicts that there is cancer cells in the matrix and their solutions indicates progression and proliferation.Without doubt, the solutions to this model equation proves that newly reproduced cancer cells are often very fast in dispersion into different parts of an organism but occasionally two or more cells may appear close to each other, thereby having enough time to divide and thus double their local concentration position because of temperature, traction force and oxidative stress action and weak immune system. From all indications, the three equations above illustrates that there is cancer initiation, progression and proliferation with time in the body of such organism a case study is Acha-Ero disease.

Here, the cancer growth rate in uniform steady state is stable to small perturbations for all $\phi(k^2)$ in equations (19) which has $\mathrm{Re}\,\phi(k^2) < 0$. It is also noticed that the cancer cells growth within a definite range of destructive rate k, can begin to grow with Re $\phi(k^2) > 0$. Also, if the cancer cells disturbances have k^2 large, with very small wavelength disturbances, then the steady state are again linearly stable. The dispersion relation therefore gives the initial rate of growth of cancer cells of various sizes.The model contains two fixed points: one of the equilibria solutions is the trivial solution with non-existence of the density fields (cell density and matrix density) and the displacement that is $(\rho_{ce}, u_e, \rho_e) = (0,0,0)$. The other equilibrium solution shows the existence of both cell density and displacement but there is no matrix density satisfies $(\rho_{ce}, u_e, \rho_e) = \left(N, \frac{\nabla\varepsilon + \nu I\nabla\theta}{s}, 0\right)$ depicting a stable and growing cancer cells in the system. Stability analysis reveals that the trivial equilibrium is a stable system showcasing tumor state while the second solution is illustrating the presence of cancer cell in the matrix with displacement.

Graphically, the oxidative stress action is on the increase showing that the cancer cells have packed up and defiled all medications by showing how they are densely packed in the matrix. The oxidative stress action in the extra-cellular matrix that leads to numerous cells packed up begins at some point after the initial stage which shows that it has lost its bonding and at point (0,0) it shows that there is no cancer cell and coalescence then it is in solid tumor state.

Conclusion

Conclusively, numerous experiments have shown that neighbor host cells tend to suppress reproduction of cancer cells by producing special biochemical substances when the immune system is strong;but when this special biochemical substances cannot be produced cancer cells reproduction is inevitable. Thus, the lower the concentration of these substances the more the reproduction of cancer cells is compressed. Thus the local concentration of cancer cells among host cells with oxidative stress and traction factor, dilation factor, secretion etc were found to be fundamental factors of their reproduction rate in this study. Cells outside a tumor when it has ruptured have a boundless access to nutrients and oxygen and thus can grow and reproduce vastly. Based on the equations above, we noted some general properties about the dispersion relation and then utilize it to promote the specific case of Acha–ero we analysed in the chapter three. The formation of the tumor–cancer cells by any morphogenetic model is primarily a nonlinear phenomenon. For further study, it can be carried out by considering the same model to tumors, or solid colonies of cancer cells; considering newly reproduced cancer cells. Anotheris the interaction between cancer cells and the immune system added with another process associated with the interaction between cancer cells and their sound neighbours. Also, point to research on is to consider cancer caused by radiation.

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