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Mathematical Model of Cellular Injury

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Abstract
This study revealed that ischemia and hypoxia are the forms of stress present in soft tissue cells that can lead to cellular injury. The study also explained that cellular injuries exhibit viscoelastic properties in the body of the living organisms as cells are damaged. The analytic solution showed that the magnitude of ischemia and hypoxia that led to cellular injury was $270\ kN$ *and the time taken for the dead cells to escalate was three months and one week. The solution showed that the environmental factor that affected the cellular injury that led to escalation of dead cells to cellular injury was temperature given as* θ *between* $80^{0} - 100^{0} c$. *The model result also showcased that the amplitude of the hypoxia in the cell damage that led to cellular injury was* $2300\ kN$ *and the time taken to enlarge was three months. Finally, the solution to the model ascertained that it took between two –three months for ischemia and hypoxia to act on a tissue cell before it ruptures and become cellular injury. All these results were determined from the graphs when plotted the parameter values given in the discussion of results. Finally, the analytic solution of the study illustrates that dead cells exist right in the rock-solid form as a result of oxidative stress (ischemia and hypoxia) losing its bonding power. The study explicate that the model equations were found in the flesh existing in a local syndrome called ''Orolla''. The system showed significant effect and was found to be stable with escalating dead cells in living organism.*

Keywords*: Cellular Injury, Stress, Ischemia, Hypoxia, Apotosis, Necrosis, Cell death.*

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I. Introduction

Cellular injury also known as cell injury or cell damage is a variety of changes of stress that a cell suffers due to external and internal environmental changes. Among other causes, this can be due to physical, chemical, infectious, biological, nutritional or immunological factors [55]. Cellular injury is also caused by stimuli which includes immunological reactions such as immune deficiency, autoimmune reactions, hypersensitivity reaction to foreign agents; nutritional imbalances such as malnutrition in protein calorie, excess intake of carbonhydrates, proteins and fats; and genetic defects such as inborn errors in metabolism [57] The causes of cellular injury are irradiation, ischemia and hypoxia as a result of oxidative stress loosing its bonding power. Hypoxia is a deficiency of oxygen which causes cell injury by reducing aerobic oxidative respiration [2,54]. It is an extremely important and common cause of cell injury and cell death. In cell biology and pathophysiology, cellular adaptation refers to changes made by a cell in response to adverse environmental changes. The adaptation may be physiological normal or pathological abnormal [56]. Five minor types of adaptation include atrophy, hypertrophy, hyperplasia, dysplasia, and metaplasia.The most important goal is to gain a general understanding of cellular adaptations or cell injury [3, 39]. The two types of cellular injury are necrosis (irreversible cellular injury) and apoptosis (reversible cellular injury or degeneration). In reversible cellular injury, stress in the cell is mild to moderate and the injured cells may recover while there is persistent and severe cell injury that can lead to cell death [1, 29]. In necrosis, mitochondria swell, lysosomes swell, plasma membrane is damaged and the lysosomal membranes lead to enzyme leakage; and there occurs acidosis protection by inhibiting enzymatic reactions [4, 20]. Cell damage depends on the extent of injury and the cellular response may be adaptive and if possible, homeostasis is restored. The study of cell injury and cell death is the basis for the understanding of disease mechanisms. Based on this cell damage, the method of damage mechanics model was adopted as to profer solution to the problem [5,40].

Thus, damage mechanics is the study done power-driven variables of the tools involved in the deterioration of materials or tissues when subjected to loading [23-26]. Damage mechanics illustrates the typical engineering methodology to model complex phenomena cellular injury. Damage mechanics shows the idea of propagation, initiation and coalescence of dead cells through the cell microenvironment under the influence of

oxidative stress in promoting cell death [37,53]. The statement of problem is to determine how dead cells of soft tissue form voids, caused the initiation and coalescence of cellular injury under the influence of ischemia and hypoxia. Thus, cellular injury it can start from any place in the body. It starts when cells grow out of control and crowd out of normal cells region which makes it difficult for the body to function the way it should. Cellular injuries behave like cancers in some ways but different in growth and spread paterns [3,37-40]. Cellular injury can move as a fluid and also as a solid when the cells are dead [36,40]. This characteristic makes cellular injury a viscoelastic material or cell. Solid growth or swollen are defined as abnormal cellular growths in the body. These sick cells crowd out healthy cells and keep them from functioning effectively [36,40].

Oxidative Stress is caused by irradiation, Ischemia and Hypoxia. In this context, the consideration will be caused by Ischemia and Hypoxia which lead to cell injury in clinical medicine. Hypoxia is the reduction of oxygen carrying capacity in the body of an organism while Ischemia which also causes hypoxia occurs due to the reduction of blood flow [52]. Hypoxia allows continuous delivery of substrates for glycolysis and slows down the removal of toxic wastes like lactic acid, H_30^+, oxygen radicals, Carbon-monoxide which accumulates to cause cell injury [4].

Ischemia stops the flow of blood nutrient and oxygen to the cells thereby starring the cells of maturation and oxygen which is another form of stress to the cells lead to cell injury called orolla. Ischemia injures tissue faster than hypoxia, thereby causing progressive compromise of multiple biochemical pathways and structural integrity of the cell in which at a point, such injury maybe compensated for and the affected cells can recover if blood flow (oxygen) is restored [51]. This type of injury is called reversible injury. Thus, at the point of no return the cells' energy generating machinery becomes irreparably damaged which is called irreversible injury [49]. At this point, it leads to amputation or mutation of the affected part of the body. In this setting, restoration of blood flow can actually exacerbate injury and that is reperfusion injury. This is clinically important in contributing to the tissue damage following myocardial infraction and stroke [44-50].

II. Literature Review

However, some scientists have carried out works on cell injury but none has used the method of damage mechanics model to profer solutions to cellular injury. One of these is the first applications of continuum mechanics to the study of growth in deformable cells; a model of homogeneous stress-dependent growth for linearly elastic cells or soft tissues developed by [20,48]. Later, a variety report of finite growth kinematics was formulated by [21,40]. The work examined volumetric growth, growth by enlargement on surfaces and growth fields with continuities or discontinuities of materials or tissues. In recent years, the phenomena of injure, deformation, alteration and escalation in soft elastic tissue cells were of interest to several researchers like [8-47]. Amongst several others, [5-42] worked on oxidative stress whereby the mitochondrial membrane becomes permeable and the signaling flow was triggered and cell injury was the end result.

However, others [11-33] worked 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. This is related to the present study in the sense that it was done on oxidative stress, disease and cancer. In these works, it showed that the ability of dead 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 injuries and diseases including cancer.

Based on the above mentioned related literatures, it is observed that the effect of ischemia and hypoxia as forms of stress in the body cells of living organisms using the method of damage mechanics model has not been modeled, analyzed and proffer solutions to the related equations. Thus, these factors will be modeled in damage mechanics as to expose the action of ischemia and hypoxia on the matrix wall of the injured cells; then how it leads to cell injury and to illustrate how the injury starts, escalates to dead cells forming cellular injury. It is this void left by researchers and the global experience of stress: ischemia and hypoxia that led the researcher to carry out a study geared towards a mathematical modeling of cellular injury.

III. Mathematical Model of Cellular Injury

From the above expounded 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 [35]. 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 [35-37, 40] that supports the equations below.

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

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

$$\frac{\partial M_\rho}{\partial t} + u_t(\nabla \bullet M_\rho) + M_\rho \bullet (\nabla u_t) = 1 - v\theta \quad (3)$$

From the above model equations (1-3) for the study, we have three dependent variables which are the density fields $C_\rho(x,t)$, $M_\rho(x,t)$ and the displacement field $u(x,t)$. The parameters involved are $D_1, D_2, a_1, a_2, \mu_1, \mu_2, r, N, \tau, \lambda, \gamma, s, E \text{ and } v$, where matrix flux is taken to be through convection and $S(n,\rho,u) = 1 - v\theta$ 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 $(M_{\rho 0})$. Setting $r^* = \frac{r}{L}$, $t^* = \frac{t}{T}$, $n^* = \frac{n}{N}$, $u^* = \frac{u}{L}$, $M_\rho^* = \frac{m_\rho}{M_{\rho_0}}$, $\nabla^* = L\nabla$,

$$\theta^* = \theta,\ \varepsilon^* = \varepsilon,\ \gamma^* = \frac{\gamma}{L^2},\ r^* = rNT,\ S^* = \frac{sM_{\rho_0}L^2(1+v)}{E},\ \lambda^* = \lambda N^2,$$

$$\tau^* = \frac{\tau m_{\rho_0} N(1+v)}{E},\ a_1^* = \frac{a_1 M_{\rho_0} T}{L^2},\ a_2^* = \frac{a_2 m_{\rho_0} T}{L^4},\quad i = 1,2,\ N_i^* = \frac{N_i(1+v)}{TE},$$

$$D_1^* = \frac{D_1 T}{L^2},\ D_2^* = \frac{D_2 T}{L^4} \quad (4)$$

The parameters have reduced to 12 parameters. If we consider T as the mitotic time of injured cells to be $\frac{1}{rN}$, then $r^* = 1$ because of our interest on the proliferation rate of injured cells on the time scale [35]. 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 equation (4) above, dropping the asterisks parameter equations (5 –7) can be solved by using the method of travelling wave solution.

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

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

$$M_{\rho,t} + \nabla \cdot (M_\rho u_t) = 1 - v\theta \quad (7)$$

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.

The model for this study is the above three equations (equations 5-7) which is seen or noticeable in a real life cell injury. This leads to the assumption of the initial boundary condition as $u = 1, C_\rho = 1, M_\rho = 1$ and that position (x) changes with time (t) which we assumed to be a constant. Since the position of cellular injury in the body starts at a point which could be any positive real number (constant) such as 1, 2, 3, …. , [37, 40]. Thus, we put $\frac{\partial u}{\partial t} = 1$ because equation (7) showed how dense the dead 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 dead cells move and also has a viscous property. From equation (7), there is no convective flux or motion. Hence, $\nabla \bullet \left(M_{\rho} u_t\right) = 0$; [36,40] therefore equation (7) reduces to

$$M_{\rho t} = 1 - \theta\nu \qquad (8)$$

Integrating w.r.t. x, t yields

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

Similarly, to solve for $C_{\rho}(x,t)$ upon integration using equation (5) gives

$$C_{\rho} = 3D_1 t\left(x_i - \frac{kt}{2}\right) - 3D_2 t\left(x_i - \frac{kt}{2}\right) - 3a_1\nu\left(\frac{x_i^2 t^2}{2} - \frac{3x_i kt^3}{2\bullet 3} + \frac{k^2 t^4}{2\bullet 4}\right) - 3a_2\nu\left(\frac{x_i^2 t^2}{2} - \frac{3x_i kt^3}{2\bullet 3} + \frac{k^2 t^4}{2\bullet 4}\right)$$

$$- 3k\left(\frac{x_i^2 t^2}{2} - x_i kt^2 + \frac{kt^3}{3}\right) - 3kt\left(x_i - \frac{kt}{2}\right) + rNt\left(x_i - \frac{kt}{2}\right) - r\left(\frac{x_i^2 t^2}{2} - x_i kt^2 + \frac{kt^3}{3}\right) \qquad (10)$$

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

$$u(x,t) = \frac{-3k\left(\chi_i^2 - 2x_i kt + k^2 t^2\right)\left(\mu_1 + \mu_2 I\right) + 3\left(x_i - kt\right)(1+\nu I) - \dfrac{27\,\tau\nu tI\left(x_i - \dfrac{3x_i kt}{2} + \dfrac{k^2 t^2}{2}\right)}{1+\lambda\left(\chi_i^2 - 2x_i kt + k^2 t^2\right)}(1+\gamma)}{s\left(t - 3\nu t x_i - \dfrac{3\nu k t^2}{2}\right)} \qquad (11)$$

Thus, the solutions to the mathematical model of cellular injury are the equations (9-11) which shows that the Extracellular Matrix density $M_{\rho}(x,t)$, cell density $C_{\rho}(x,t)$ 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.

IV. Discussion of Results

When this model is simulated with the parameter values below $\nu = 0.2$, $\chi_1 = 1$, $k = 0.5$, $t = 0:5:100$ using equation 9, the end result showed the graph of matrix density, M_{ρ} against time, t in months with arbitrary values of x_1. The graph portrays that the matrix is quadratic in t and the existence of injured cells in the matrix gave rise to exponential rise in the time taking for the density to increase. In terms of the time, it showed that the lower the time the lower the matrix density and as the time increases the injured cells in matrix density also increases. When plotted, the graph depited that the matrix volume is 50mm^3 in 10days.

Equation 10 when the graph of cell density against time was plotted with these arbitrary Values: $D_1 = 1$, $D_2 = 0.6$, $\chi_1 = 1$, $k = 0.5$, $r = 0.8$, $N = 1$, $t = 0:5:100$ showed that the cell density at different values of position (x_1) linearly increases as the time increases. This also explained the intensity of the stress action in growing the dead cells harboured by the matrix thereby making it to be densely packed and is linearly directly to the time in months it takes to spread or proliferate in the matrix of an organism. At this point, the oxidative stress bonding action has vanished in the body of the organism, showing that more dead cells are packed in the matrix in a linear direction.

When the arbitrary Values: $\mu_1 = 1$, $\mu_2 = 0.4$, $\chi_1 = 2.1$, $k = 0.5$, $\tau = 0.7$, $I = 1$, $\gamma = 0:5:100$, $\lambda = 0.5$, $s = 10^6$, $\nu = 0.2$, $r = 0.8$, $N = 1$, $t = 2$ are used to plot the graph of

displacement against gama in months (i.e.magnitude of the wound in the matrix of the organism). The graph depicted that hypoxia and ischemia have occurred (the reduction of oxygen carrying capacity and blood flowin the body of an organism). There is no displacement and dead cells at point (0,0) because the wound is still in its suspression state.

The arbitrary Values: $\mu_1 = 1$, $\mu_2 = 0.4$, $\chi_1 = 2.1$, $k = 0.5$, $\tau = 0.7$, $I = 1$, $u = 0:5:100$ $\lambda = 0.5$, $s = 10^6$, $\nu = 0.2$, $r = 0.8$, $N = 1$, $t = 2\sec s$, $\gamma = 0.7$, were used to plot the graph of oxidative stress action against the displacement of the dead cells in the body of the organisms (matrix). This action at position (x1, x2, x3) showed that hypoxia and ischemia linearly increases the rate of dead cells with changes in position. The graph also explained the intensity of hypoxia and ischemia action on human cells thereby causing displacement, but at zero point it is minimal because there is no wound for it to act upon. Hence, the oxidative stress value increases showcasing that the dead cells have defiled all medications and are densely packed in the matrix wall of an organism. Thus, at the point of no return the cells' energy generating machinery becomes irreparably damaged which is called irreversible cellular injury. In this setting, restoration of blood flow can actually exacerbate injury and that is reperfusion injury.

When these values: $\tau = 0.7$, $\rho = 1.2 \times 10^{-2}$, $\lambda = 30$, $I = 0.3$, $\chi_1 = 2.1$, $\chi_2 = 2.4$, $\chi_3 = 3.0$, $k = 0.5$, $t = 0:5:100$, were used and plotted which depicted the effects of oxidative stress against time taken (in months) in the matrix of the organism for the volume to increase as it harbours dead cells. Hence, the model solution also ascertained that it took between 2 –3months for the hypoxia and ischemia to act on a tissue cell before it leads to cell injury. This means that at the point, hypoxia allow continuous delivery of substrates for glycolysis and slow down the removal of toxic wastes like lactic acid, H_30^+, oxygen radicals, Carbon-monoxide which accumulates to cause cell injury. And also, Ischemia stops the flow of blood nutrient and oxygen to the cells thereby starring the cells of maturation and oxygen which is another form of stress to the cells that causes cell injury.

V. Conclusion

Conclusively, this study revealed that ischemia and hypoxia are the forms of stress present in soft tissue cells that can lead to cellular injury. Some scientific experiments have shown that neighbouring host cells tend to inhibit increase in dead cells by producing special biochemical substances when the body immunity is strong. However, when the body can not produce special biochemical substances reproduction of dead cells and cellular injury is unavoidable. For further areas of research, same study can be carried out by considering the same model to cellular injury with treatment, cell injury in the form of solid colonies of dead cells and cell injury caused by radiation.

DEFINITION OF PARAMETERS

N	*Maximum number of dead cell in the injured area*
$\sigma(x,t)$	*Stress tensor*
x	*Position*
t	*Time*
f	*Body force*
$M_\rho(x,t)$	*Density of the ECM*
$C_\rho(x,t)$	*Cell density*
$C_{\rho,t}$	*Partial differentiation of cell density w.r.t, t*
∇	*Laplacian operator*
$n(x,t)$	*Number of cells per unit volume*
$u(x,t)$	*Displacement vector of the matrix*
D_1, D_2	*Diffusion parameters*
μ_1, μ_2	*Shear and bulk viscosities of the ECM*
a_1, a_2	*Long range effect for mechanotaxis flux*
τ	*Cell traction force*
θ	*Dilation*
ε_t	*Partial differentiation of strain tensor w.r.t. t*

θ_t	*Partial differentiation of dalition w.r.t. t*
u_t	*Partial differentiation of displacement w.r.t. t (velocity of deformation of matrix)*
n_t	*Partial differentiation of cell density w.r.t. t*
$M_{\rho,t}$	*Partial differentiation of density of the ECM w.r.t. t*
γ	*Measure of the nonlocal long range cell-ECM interactions*
r	*Initial proliferative rate in cell death*
I	*Unit tensor*
S	*Elastic parameter for the substrate attachments*
$\boldsymbol{\lambda}$	*Parameter that controls the activator of dead cell growth (hypoxia)*
V	*Poisson ratio*

Table 1: Description of variables and parameters in the model

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